Hypotension during hemodialysis

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Noninvasive monitoring of hemodynamic variables

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promotor: prof.dr. P.M. ter Wee

copromotor: dr. P.M.J.M. de Vries

It may be one small step for mankind, it's a giant leap for one man

Vrij naar Neil Armstrong (1930), 20 juli 1969

Voor mijn ouders

Contents

BIA	bioimpedance analysis
BP	blood pressure
BV	blood volume
BVM	blood volume monitoring
CI	cardiac index
CO	cardiac output
ECW	extracellular water
EIC	electrical impedance cardiography
ESRD	end stage renal disease
H	hypotensive patient group
HD	hemodialysis
HR	heart rate
HRV	heart rate variability
Ht	hematocrit
I	current
ICW	intracellular water
IDH	intradialytic hypotension
MAP	mean arterial pressure
Non-H	non-hypotensive or stable patient group
R	resistance
SD	standard deviation
SEM	standard error of the mean
SV	stroke volume
SVR	systemic vascular resistance
TBW	total body water
UF	ultrafiltration
V	voltage
Xc	reactance
Z	impedance

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General introduction

INTRODUCTION

Background

Hemodialysis (HD) is available since the early 1950's and has gained tremendous technical improvements since then. To date, there are approximately 9500 end-stage-renal-disease (ESRD) patients in the Netherlands. Thirty-five percent of them is depending on some form of hemodialysis. On average, this means that they are treated thrice weekly during a 4-hour session. Hemodialysis treatment is accompanied by a wide variety of complications. The dialysis population is changing over the years, increasing in age and comorbidity, such as diabetes mellitus, affecting cardiovascular stability.
Despite all technical improvements, one of the most frequent complications remains intradialytic hypotension (IDH), occurring in up to 20% of dialysis sessions. IDH is defined as a symptomatic decrease of more than 30 mmHg in systolic blood pressure or as an absolute systolic blood pressure under 90 mmHg. Decades of research revealed that the cause of IDH is multifactorial. First described in 1970 (1), Bergström showed in 1978 that intravascular hypovolemia, due to a large volume of ultrafiltration in too short a period of time, was not the sole cause of IDH (2). There is a difference in blood pressure stability between isolated ultrafiltration and hemodialysis (3). Hemodialysis is the combination of ultrafiltration of fluid excess and the clearance of solute waste products such as urea by diffusion. Dialysis without ultrafiltration rarely causes IDH. Therefore, it can be concluded that IDH occurs when normal compensatory mechanisms cannot cope with the removal of intravascular fluid in a short period of time in a specific patient.
Negative effects of IDH are the discomfort for the patient and the decline in efficacy of HD due to interventions such as interruption of HD and the necessity for intravenous infusions. More importantly, a recent study reports increased mortality in hypotension prone hemodialysis patients (4). Therefore, reducing intradialytic hypotension remains a challenge. The factors playing a role in the pathogenesis of IDH will be outlined. Patient related data will prove to be essential in this dilemma.
This thesis is aimed at collecting and interpreting bedside hemodynamic parameters, to define the pathogenesis of IDH and thereby to apply the most appropriate protective strategies for the hypotension prone hemodialysis patient on an individual basis.

Normal compensatory response on hemodialysis.

In end stage renal disease (ESRD) patients, fluid accumulation will occur between two hemodialysis sessions. This excess fluid will be situated mainly in the extracellular compartment and has to be removed during a hemodialysis session. Often the amount of fluid that has to be removed equals the amount of the plasma volume and has to be withdrawn from the intravascular compartment within a short period of time. During hemodialysis fluid will be removed from the intravascular compartment by ultrafiltration resulting in a loss of iso-osmotic fluid (water and solutes). Thus, intravascular hypovolemia may ensue from intravascular fluid and solute loss. There are several mechanisms counteracting the consequent relative intravascular hypovolemia, thereby aiming to preserve adequate blood pressure. Failure of these compensatory mechanisms leads to intradialytic hypotension.

Plasma refilling

To maintain adequate blood pressure, capillary plasma refilling counteracts ultrafiltration induced hypovolemia. Plasma refilling from the extracellular compartment towards

the intravascular compartment is driven on the one hand by a reduced intravascular hydrostatic pressure due to the loss of iso-osmotic fluid and, on the other hand, due to an increased intravascular oncotic pressure due to ultrafiltration resulting in a rise in serum albumin. Because there is some delay in refilling, the magnitude of intravascular hypovolemia is influenced by the rate and amount of the ultrafiltration volume. The hereby induced relative hypovolemia plays a central role in subsequent intradialytic complications such as hypotension (5). The magnitude of the intravascular hypovolemia can be reduced by minimizing the volume necessary to be withdrawn. The ultrafiltration volume is determined by the interdialytic weight gain. Thus, aiming at the smallest interdialytic weight gain achievable by the patient is of supreme importance. Furthermore, an adequate assessment of the dry weight to be achieved at the end of HD is essential.

Cardiac adjustment
Normal compensatory cardiac mechanisms to prevent hypovolemia are an increase in heart rate and contractility. During hypovolemia an increase in heart rate, caused by beta-adrenergic activation, is of relatively minor importance in maintaining blood pressure (6). Thus, diminished ability to increase contractility will cause increased sensitivity to hypovolemia. In addition, there is a high prevalence of congestive heart failure in ESRD patients (7). Due to chronic fluid and pressure overload, left ventricular hypertrophy is frequently present. This typically causes diastolic dysfunction, resulting in an unusual sensitivity to changes in intravascular volume (8). When the venous return to the heart is diminished, the ventricles will contract around an almost empty chamber, thereby eliciting the Bezold-Jarisch reflex. This is a cardio-inhibitory reflex to prevent myocardial damage in case of extreme intracardial hypovolemia (9). The resulting bradycardia together with the present hypovolemia may cause hypotension. Thus, the effect of a less compliant heart is augmented in a situation of hypovolemia. This results in increased risk of IDH in cardiac compromised patients.

Venous tone
Centralization of blood volume during hypovolemia occurs by means of passive venoconstriction. This is called the De-Jager-Krogh phenomenon, meaning that due to diminished arterial blood supply in a state of hypovolemia, venous capacitance beds will contract because of reduced distending pressure, thereby preserving cardiac filling (10,11). When arteriolar vascular resistance fails to increase, the distending pressure transferred to the capillary and venous system is preserved. Passive recoil of the venous capacitance bed will be impeded, thereby diminishing venous return to the heart and thus cardiac filling.

Systemic vascular resistance
Active arterial vasoconstriction preserves blood pressure. Adequate autonomic function is necessary to enable vasoconstriction. During uncomplicated hemodialysis, no change in autonomic function is observed (12). However, general autonomic neuropathy is frequently present in ESRD patients, and a relation between autonomic neuropathy and IDH was already suggested in 1974 (13,14). In HD complicated by hypotension, a paradoxical sympathetical withdrawal was reported (15), possibly as a result of activation of the Bezold-Jarisch reflex caused by critical cardiac underfilling. Another factor reported to play a role is release of counterproductive vasodilating substances during hemodialysis. For instance, adenosine is thought to be released during tissue ischemia, occurring un-

der hypovolemia (16). Nitric oxide (NO), a potent vasodilator, is shown to be increased in dialysis hypotension (17,18). The etiology of this release of vasodilating agents has not been clarified.

For years IDH is thought to be multifactorial in its origin. Different aspects of normal compensatory responses can fail, causing intradialytic hypotension. Because of the close interactions between the several blood pressure regulating mechanisms, disentangling the origin of the hypotension can be difficult. The main focus has been on dialysis-related aspects, currently shifting towards patient-related aspects. With a hemodialysis population increasing in age and comorbidity, patient-related causes of IDH become more important. Therefore, bedside patient-related information is needed in order to influence dialysis related parameters, aiming at alleviating IDH for the individual hemodialysis patient and mitigating the detrimental effect on dialysis efficacy and, thereby, improving long term survival.
Described below are the noninvasive techniques, by means of which we measured or derived the most important hemodynamic parameters. Blood pressure was measured by an automatic cuff sphygmomanometer. Simultaneously stroke volume and heart rate are monitored by means of electrical impedance cardiography. Thus, cardiac adjustments before and during hypotensive episodes could be interpreted. Vascular resistance response were determined from changes in cardiac output in comparison to blood pressure changes. Together with impedance-derived calculation of extracellular water and total body water, concomitant blood volume and ultrafiltration monitoring provided information about volume status and the degree of hypovolemia.

Methods

Electrical Impedance Cardiography (EIC)

Electrical Impedance Cardiography is a method to non-invasively measure cardiac stroke volume. It is based on Ohm's law: $V = I * R$, i.e. voltage is electrical current strength times resistance. When a current with a known strength is applied between two electrodes and the voltage is measured, resistance can be calculated. When an alternating current is used, resistance is called impedance (Z). The human thorax can be considered as a conductive structure of which the thoracic tissues provide a basic impedance signal and the pulsatile blood flow provides a superimposed changing signal. Since the intrathoracic blood volume increases with every cardiac ejection, the thereby decreasing impedance reflects stroke volume. This beat-to-beat impedance variation can be averaged over a period of heartbeats, resulting in a specific waveform signal (Figure 1).
With the equation of Kubicek (19,20), stroke volume can be calculated from the first derivative of this signal. In practice, to obtain impedance changes over the thorax due to cardiac activity, four electrode levels are applied in a 9-electrode configuration as described by Woltjer et al. (21) (Figure 2). The outer two levels are the current applying electrodes and the inner two levels detect the voltage changes over the thorax: two electrodes are placed at the base of the neck and two electrodes in the midaxillary lines at the level of the xiphoid. All electrodes in one level being electrically connected, an alternating current of 0.8 mA RMS and 60 kHz is passed through the current applying electrodes and impedance is calculated using Ohm's law. Simultaneously with the impedance recordings, lead I of the ECG is recorded and mean arterial blood pressure (MAP) is measured every 10 minutes using a cuff sphygmomanometer. Cardiac output (CO) is calculated as stroke volume (SV) times heart rate (HR), and systemic vascular resistance

(SVR) as (MAP/CO) * 80, expressed as dynes/s/cm^{-5}. Thus, a complete hemodynamic impression can be obtained during hemodialysis, especially interesting around hypotensive episodes.
The technique has been thoroughly validated under various conditions and compared to thermodilution, the golden standard of stroke volume measurement (22-27). Also during hemodialysis EIC proved its value (28,29). Despite the extensive validation studies, the technique has not been generally accepted for hemodynamic monitoring during HD thus far. Few studies have used EIC to clarify individual causes of IDH (28-30). However, several recent studies encourage the use of EIC in different clinical settings, such as the Cardiology and the Emergency Departments (31-34). In this thesis the value of EIC in hemodialysis patients will be re-emphasized.

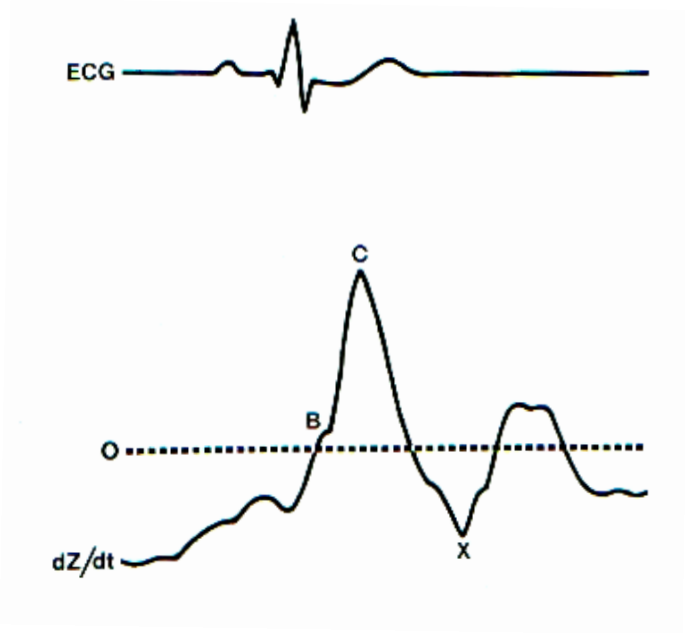

Figure 1. *Characteristic signal of Electrical Impedance Cardiography*

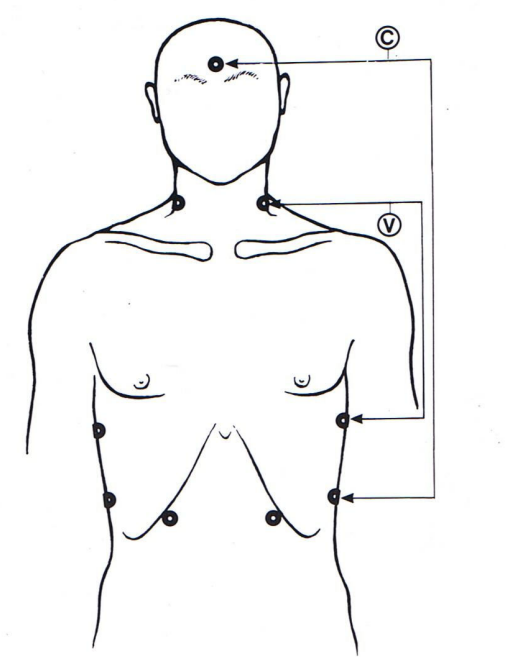

Figure 2. *Electrode configuration in Electrical Impedance Cardiography*

Continuous blood volume monitoring (BVM)
Assuming that changes in blood volume during HD only occur because of extracorporeal ultrafiltration and vascular refilling, blood volume will decrease when the ultrafiltration rate exceeds vascular refilling rate. An optical device was used in order to monitor variations in blood volume during HD continuously and non-invasively, as described by De Vries et al. (35). This method is based on the principle of infrared light propagation in whole blood. A part of this light will be reflected by erythrocytes as a result of scattering (36). The amount of reflected light detected is directly proportional to the concentration of blood cells in whole blood. Because erythrocyte concentration is reciprocally related to blood volume, the variations in blood volume can easily be calculated using the data derived from the optical device. It has been hypothesized that continuous monitoring of blood volume changes can reduce intradialytic symptoms by setting an individual hematocrit threshold (37). On the other hand, IDH has been shown to occur even with minimal blood volume decrease, emphasizing the multifactorial character of IDH (38).

Bioimpedance Analysis (BIA)
Dry weight is an important parameter in hemodialysis, because the ultrafiltration volume is the difference between the actual predialysis weight and the assumed dry weight, achieved post dialysis. Clinical assessment still plays a major role in this determination. Several techniques have been studied to assess dry weight more objectively and more accurately. Echocardiography of the inferior vena cava has been mentioned as a reliable tool (39,40). Bioimpedance analysis has also proven to be a promising method for determining dry weight (39,41).
With four electrodes applied over the wrist and the ipsilateral ankle an electrical field is induced in the patient. Total body resistance (R) and reactance (Xc) can be calculated from the measured voltages. The resistance is directly correlated to total body water and the reactance to intracellular water. Thus, the hydration state can be monitored noninvasively. Combined with hemodynamic parameters during hemodialysis, this provides more insight in fluid shifts caused by hemodialysis. For instance, the degree of blood volume decrease in relation to ultrafiltration volume is a measure for capillary refill rate and signals the presence of over- or underhydration. Furthermore, post dialysis dry weight can be established more accurately by using reference values for normohydration in healthy subjects.

Aims of the study
Identifying the most prominent cause of IDH in every hypotension prone patient individually may lead to a tailor-made, individualized dialysis strategy. Measuring hemodynamic parameters in the individual patient provides the opportunity to classify the patient in different risk categories, enabling specific therapy.
What is needed is bedside patient-related information in order to influence dialysis related parameters, aiming at alleviating IDH for the individual HD patient and mitigating the detrimental effect on dialysis efficacy and, thereby, improving long-term survival. Gathering reliable hemodynamic parameters during frequent short sessions, without extra burden for the dialysis patient, is difficult. Electrical Impedance Cardiography (EIC) provides a tool for noninvasive bedside monitoring of intradialytic hemodynamics.

In **chapter 2** we describe several hemodynamic changes *during* hemodialysis leading to hypotension using noninvasive monitoring devices. Alterations in blood volume are measured, as well as changes in stroke volume (SV) and heart rate (HR), forming cardiac output (CO). Combined with blood pressure measurements, responses in systemic vascular resistance can be calculated. Description of these hemodynamic changes during dialysis will reveal more about the initiation of hypotension and the factors affecting it.

Chapter 3 is aimed at subgroup analysis of hypotension prone patients. An attempt will be made to provide a classification of the individual hypotension prone patient into different causal categories. Since several preventive strategies are available, subgroup classification might enable more specific preventive strategies based on actual measurements.

Before applying individualized strategies, it is important to know whether these individual causes are reproducible within different IDH episodes. Therefore, in **Chapter 4** the reproducibility of the classification of the cause of the hypotensive episode will be studied for the individual patient. Several dialysis sessions per patient will be monitored to assess reproducibility of hypotension mechanism.

Chapter 5 describes the quality of the autonomous nervous system in rest in hy-

potension prone and stable hemodialysis patients. By means of several autonomous function tests several parts of the autonomous nervous system are assessed. This study aims to identify wheather structural abnormalities in autonomous nervous function play a role in causing IDH.

Finally, in **chapter 6** a frequently applied preventive strategy, sodium profiled hemodialysis, is tested in its ability to change hemodynamic variables in a beneficial way. Attention is paid to avoiding sodium overload, which increases thirst and thereby interdialytic weight gain.

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2

Systemic vascular resistance in intradialytic hypotension determined by means of impedance cardiography

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ABSTRACT

Background. Recurrent intradialytic hypotension still is a major source of discomfort in hemodialysis patients today, its origin being subject to extensive research. Different hypotheses have been raised to unravel this problem, without forming one coherent point of view. The aim of this study was to gain more insight in the mechanisms causing intradialytic hypotension by determining cardiovascular performance non-invasively during hemodialysis in a large group of patients.

Methods. In the present study the variations in blood volume, stroke volume, cardiac output and systemic vascular resistance were investigated in sixty-eight patients on chronic intermittent hemodialysis utilizing bioelectrical impedance cardiography. In addition, blood volume was monitored continuously with an on-line optical device.

Results. Twenty-four patients experienced a symptomatic hypotension during dialysis treatment. Compared to the hemodynamically stable patients, the hypotensive patients manifested a slightly greater decline in blood volume (mean ± SEM: -9.4 ± 1.2 vs. -6.5 ± 0.8%, $P = 0.04$) and cardiac output (-11.8 ± 4.2 vs. -7.3 ± 2.7%, P = NS). The main difference, however, was a highly significant decrease in systemic vascular resistance (-17.9 ± 4.4%) in the hypotensive group compared to a rise in the stable group (+6.2 ± 3.5%, $P < 0.001$).

Conclusion. Intradialytic hypotension seems the consequence of an inadequate compensatory response to ultrafiltration-induced blood volume reduction, resulting in a fall in systemic vascular resistance. The degree of hypovolemia itself appears to be less important in the origin of acute, intradialytic hypotensive episodes. Non-invasive monitoring during hemodialysis provides an opportunity to gain more insight in the pathophysiology of intradialytic hypotension and offers the possibility for controlled intervention and possible prevention of this complication.

INTRODUCTION

Intradialytic hypotension is a major complication in end stage renal disease (ESRD) patients on chronic intermittent hemodialysis (HD). Despite worldwide efforts to understand their background, up to 30% of these patients still suffer frequently from hypotensive episodes that require intervention and reduce dialysis efficacy (1). Increasing knowledge of intradialytic hypotension is of great importance for HD patients, since understanding the process completely may lead to earlier detection and perhaps even prevention. Several factors contribute to dialysis hypotension, of which hypovolemia has long been considered to be the most important factor (2-4). Nowadays, the emphasis is shifting more and more towards failing compensatory mechanisms. The two most important compensation mechanisms are the ability of the heart to maintain cardiac output and a rise in systemic vascular resistance (SVR). Ritz suggested a diastolic left ventricular dysfunction (5), whereas others claimed a role for vasodilating agents such as nitric oxide (6). A third option is sympathetic withdrawal during dialysis (7).
Over the past few decades, electrical impedance cardiography has been developed to a non-invasive method to assess stroke volume (SV) and cardiac output (CO) (8). The technique determines the thoracic impedance changes resulting from the pulsatory cardiac pump function. Because of the possibility to perform measurements at the bedside, electrical impedance cardiography is suitable for monitoring of SV and CO during HD (9). The purpose of the present study was to investigate hemodynamic interactions during hemodialysis in order to specify which (patho)physiological mechanisms underlie the occurrence of symptomatic hypotensive episodes during HD. Therefore, we studied 68 patients on chronic intermittent hemodialysis during one HD session by means of electrical impedance cardiography to obtain non-invasively values for SV, CO and SVR. In addition, a continuous on-line blood volume monitor was used to visualize changes in blood volume (BV).

SUBJECTS AND METHODS

Subjects

A group of 68 patients (38 males; 30 females) on chronic intermittent hemodialysis was included in the study. All patients were dialyzed 9-15 hours per week divided over 2-3 sessions with biocompatible polysulfone membranes, using bicarbonate as buffer and heparin as anticoagulant. Blood flow varied from 180 to 300 ml/min, whereas the dialysate flow was 500 ml/min and the dialysate sodium concentration 141 mmol/L. Dry body weight was determined individually by the attending physician on clinical grounds such as blood pressure, peripheral and/or pulmonary edema, and central venous pressure. Ultrafiltration (UF) volume was based on the difference between pre-dialysis and dry weight. Patients experiencing a decrease in supine systolic blood pressure during dialysis of 30 mmHg or more, or an absolute blood pressure less then 90 mmHg, were defined as hypotensive and classified as group *H*, whereas stable patients formed group *non-H*. To minimize confounding, cardiovascular medication was withheld on the day of dialysis. Withdrawal of this medication during a larger period was clinically not acceptable. Patient characteristics of the two groups are given in Table 1. All patients gave their informed consent.

Table 1. *Characteristics of the hemodynamically stable (non-H) and the hypotension-prone (H) patients.*

	non-H	H	p
Number	44	24	
Sex (f/m)	19/25	11/13	NS
Age (years)	54 (2.9)	58 (3.5)	NS
Dry weight (kg)	63.4 (2.3)	68.4 (3.3)	NS
Diabetes Mellitus	2/44	4/24	NS
Antihypertensive Drugs	25/44	18/24	NS
History of HD (months)	58 (9.1)	40 (8.5)	NS

All values are expressed as their mean (SEM). HD = hemodialysis; NS = not significant

Impedance cardiography

Impedance cardiographic measurements were performed using the IPG-104 impedance Mini-Lab (RJL Systems, Detroit, USA, and Equip Medikey, Gouda, The Netherlands). The patients were measured every hour or when symptoms of hypotension occurred, such as dizziness, frequent yawning or perspiration. The time interval was calculated from the start of dialysis until the moment of hypotension for the H group, and compared with the non-H group from the start of dialysis until the measurement on average closest to the moment of hypotension in the H group.

To obtain impedance changes over the thorax due to cardiac activity, four electrode levels were applied according to Woltjer et al. as is shown in Figure 1 (10). The outer two levels were the current applying electrodes: the cranial level consisted of one electrode on the forehead, whereas the caudal level consisted of four electrodes placed semicircularly on the lower part of the abdomen, two in the midaxillary lines and two in the midclavicular lines. The inner two levels detected the voltage changes over the thorax: two electrodes were placed at the base of the neck and two electrodes in the midaxillary lines at the level of the xiphoid. All electrodes in one level being electrically connected, an alternating current of 0.8 mA RMS and 60 kHz was passed through the current applying electrodes and impedance (R) was calculated using Ohm's law (R = V / I; where V = measured voltage and I = strength of alternating current). All data were digitally stored and 20 consecutive heart cycles were averaged by means of our data acquisition system, after which signal variables were manually assessed as described by Lababidi et al. (11). Finally, SV was calculated with the equation of

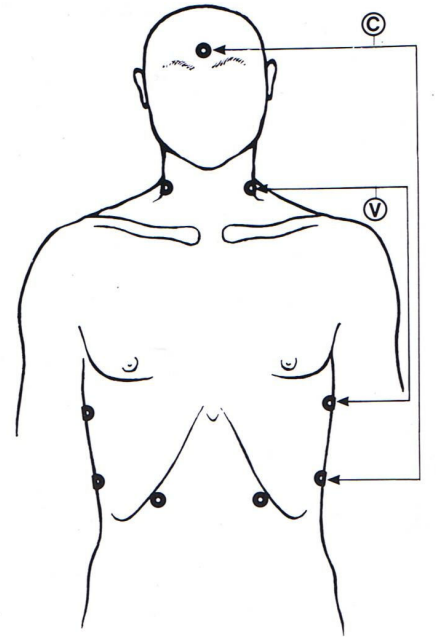

Figure 1. *Electrode configuration for electrical impedance cardiography: c = current applying electrodes and v = voltage detecting electrodes.*

Kubicek (12). Simultaneously with the impedance recordings, lead I of the ECG was recorded and mean arterial blood pressure (MAP) was measured every 10 minutes using a cuff sphygmomanometer. CO was calculated as stroke volume (SV) times heart rate (HR), and SVR as (MAP/CO) * 80, expressed as dynes/s/cm^{-5}. To assess reproducibility, Mehlsen and colleagues tested 62 measurements of cardiac output in a range from 2.95 to 10.16 l/min (mean 5.76 l/min) and the standard deviations were 0.33 l/min (the inter-observer variation) and 0.12 l/min (intra-observer variation) (13). It was concluded that impedance cardiography is reliable in measuring changes in cardiac output and therefore suitable for repeated measurements as in our study. Because aortic valvular pathology appeared to produce less reliable CO values (14), these patients were excluded from the present study.

Blood volume monitoring

An optical device (Critline®, In-Line Diagnostics, Riverdale (Utah), USA) was used in order to monitor variations in blood volume during HD continuously and non-invasively, as described by De Vries et al. (15). This method is based on the principle of infrared light propagation in whole blood. When monochromatous near infrared light is transmitted through blood, three processes occur: a part of the light will pass through the blood unimpeded, another part will be absorbed by blood components, among which hemoglobin is the most important, and a third part will be reflected by erythrocytes as a result of scattering (16,17). The amount of detected reflected light is directly proportional to the concentration of blood cells in whole blood. Because erythrocyte concentration is reciprocally related to blood volume, the variations in blood volume can easily be calculated using the data derived from the optical device. The measuring probe of this device, placed at the arterial side of the dialyzer, consists of a light-emitting diode and a light-detecting receiver. The calculation is performed by a small computer and shown graphically on a display. Blood samples were taken every hour for laboratory assessment of erythrocyte concentration. Ultrafiltration was held constant during HD. Assuming that changes in blood volume during HD only occur because of extracorporeal ultrafiltration and vascular refilling, blood volume will decrease when the ultrafiltration rate exceeds vascular refilling rate.

Statistical analysis

Differences between the two groups were analyzed by means of the unpaired Student's *t* test, and between different time intervals within one group by means of the repeated measures analysis of variance. The relationship between different variables was evaluated using linear regression analysis. Interdependency between variables was tested by multiple regression analysis. Chi square tests were performed to express the difference in the distribution of cardiovascular medication and sex. P values < 0.05 were considered significant.

RESULTS

In 24 (13 males; 11 females) out of the 68 patients a symptomatic hypotensive episode occurred, requiring temporarily UF cessation, and infusion of an isotonic saline or a hyperosmotic gelatin solution (Gelofusin®) if necessary. The distribution of cardiovascular medication in the hypotensive and the stable group was not significantly different ($p > 0.1$; Table 1). The hypotensive episodes occurred on average 198 minutes (SEM ± 9 min) after the start of HD, and were compared to the t=180 min. measurement in the non-H

group. No significant differences were observed between the t=180 and the t=240 min. measurements in the non-H group, except for the decrease in BV (t=180: -6.5 ± 0.8% vs. t=240: -8.7 ± 0.9%, p < 0.001). During these hypotensive episodes MAP decreased from 96 to 66 mmHg (SEM ± 2.6) in the H group, whereas at the corresponding moment in the non-complicated dialysis sessions MAP amounted to 96 mmHg (SEM ± 2.2). In Table 2 the changes of the hemodynamic variables in the two groups are provided. All data analyses with mean arterial pressures were also performed with systolic and diastolic blood pressures and did not change any results. Multiple regression analysis was performed to test the dependency between the change in MAP (dMAP) and the changes in

Table 2. *Changes in hemodynamic variables in the hemodynamically stable (non-H) and the hypotension-prone (H) patients from the start of treatment until the average time of hypotension (or the similar moment in the non-H group).*

	non-H	H	*P*-value
Number	44	24	
dMAP (%)	-4.8 (1.6)	-30.5 (3.0)	<0.001
dSVR (%)	6.2 (3.5)	-17.9 (4.4)	<0.001
dCO (%)	-7.3 (2.7)	-11.8 (4.2)	0.35
dSV (%)	-10.8 (3.0)	-21.1 (4.1)	0.04
dHR (%)	5.7 (2.5)	13.1 (2.9)	0.07
dBV (%)	-6.5 (0.8)	-9.4 (1.2)	0.04

All values are expressed as their mean (SEM).

Table 3. *Absolute values of hemodynamic variables at the start, at the hypotensive episode (H) or corresponding moment (non-H), and at the end of dialysis in hypotensive (H, n = 24) and non-hypotensive (non-H, n = 44) patients.*

	non-H			*H*		
	start	3 h.	end	start	H	end
MAP (mmHg)	102 (2.2)	96 (2.2)	97 (2.4)*	96 (2.6)	66 (2.6)[1]	75 (3.0)[1,*]
CO (l)	4.6 (0.3)	4.2 (0.3)	4.0 (0.3)*	3.9 (0.4)	3.4 (0.3)	3.2 (0.3)[2,#]
SV (ml)	62.9 (3.8)	56.1 (3.7)	52.9 (3.5)*	54.5 (5.6)	41.6 (4.1)[2]	40.5 (3.8)[2,*]
HR (bpm)	73 (1.6)	76 (1.6)	78 (1.9)[#]	75 (2.7)	84 (3.1)[2]	84 (3.0)*
SVR (§)	2152 (164)	2282 (213)	2347 (208)	2373 (222)	1907 (206)	2187 (235)*
Ht (%)	33.5 (0.6)	35.7 (0.7)	36.6 (0.7)*	33.9 (0.9)	37.6 (1.0)	37.2 (1.0)*
UF (l)	0	2.1 (0.1)	2.7 (0.1)	0	2.8 (0.2)[1]	3.1 (0.2)[2]

*All values are expressed as their mean (SEM). §: dynes/s/cm^{-5}; * P < 0.001 within group (ANOVA); [#] P < 0.05 within group (ANOVA);[1] P < 0.001 compared to non-H; [2] P < 0.05 compared to non-H.*

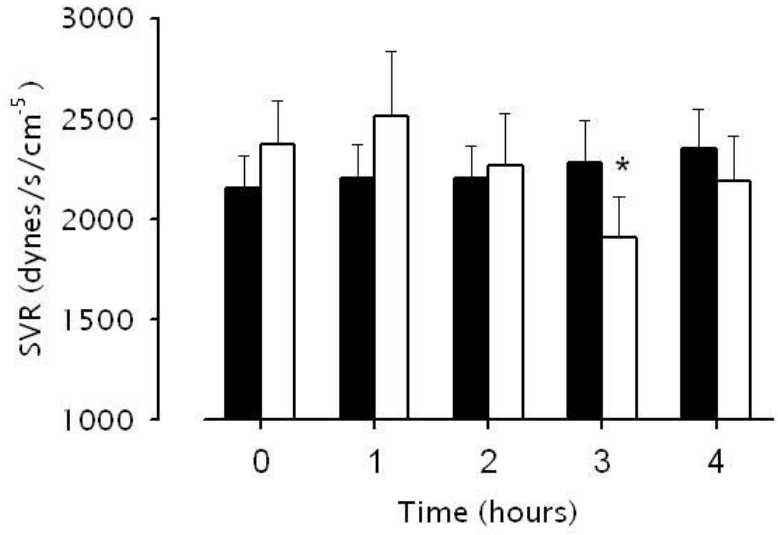

Figure 2. *Systemic vascular resistance index (mean ± SEM) during hemodialysis. Note that t = 4 in group H is after intervention. Open bars = H, closed bars = non-H, * = P < 0.001 compared to t = 0.*

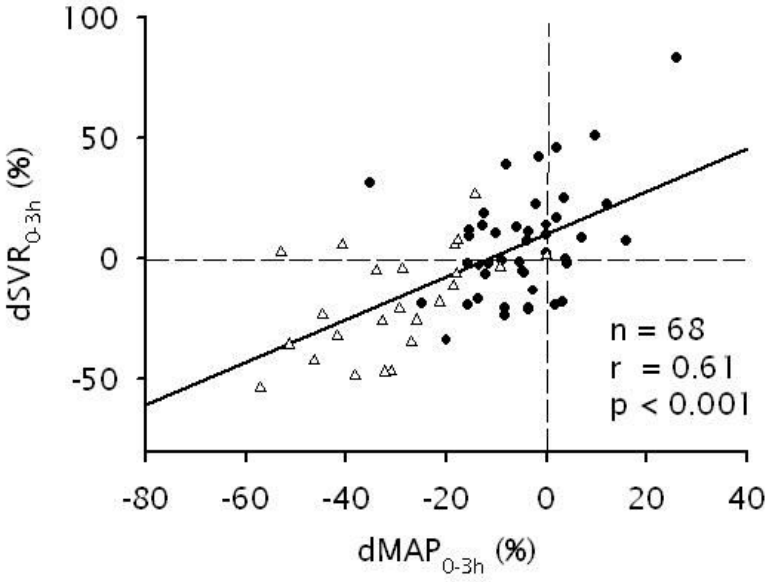

Figure 3. *Correlation between change in systemic vascular resistance (dSVR) and change in mean arterial pressure (dMAP) from the start of dialysis until the moment of hypotension or the similar moment in the non-H group. • = non-Hypotensive group; Δ = Hypotensive group.*

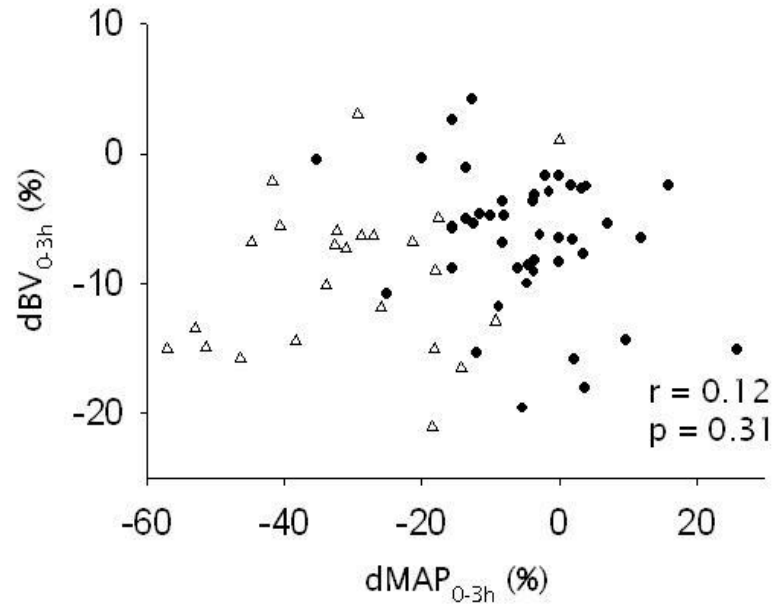

Figure 4. *Correlation between change in BV (dBV) and change in mean arterial pressure (dMAP) from the start of dialysis until the moment of hypotension or the similar moment in the non-H group. • = non-Hypotensive group; Δ = Hypotensive group.*

hemodynamic factors determining MAP, such as dSVR, dSV, dHR and dBV. It revealed an association between dSVR and dMAP in both the H group (ß = 1.23, p < 0.001) and the non-H group (ß = 1.52, p < 0.001).
The most significant difference between the two groups was a change in systemic vascular resistance from the start of dialysis until the moment of hypotension (H -17.9 ± 4.4% vs. non-H +6.2 ± 3.5%, p < 0.001). Figure 2 shows the change in SVR occurring from hour to hour in both groups. The Pearson's correlation between changes in SVR and MAP (Figure 3) was highly significant in the whole group (r = 0.61, p < 0.001), as well as in the H group (r = 0.55, p = 0.006) and the non-H group (r = 0.41, p = 0.005).
The UF volume at the moment of hypotension (see Table 3) was higher in the hypotension-prone patients (2.8 l) compared to the UF volume at the corresponding moment in hypotension-resistant patients (2.1 l, p < 0.001), which corresponded with a significantly steeper fall in BV (-9.4% in H vs. -6.5% in non-H, *P* = 0.04), suggesting a more pronounced hypovolemia in hypotensive patients. However, changes in BV did not correlate with changes in MAP neither in the whole group (r = 0.12, p = 0.31) (Figure 4), nor in one of the subgroups (H: r = 0.18, p = 0.39; non-H: r = -0.29, p = 0.06). Multiple regression analysis revealed no significant dependency between dMAP and dBV, neither between dSVR and dBV. BV variation recorded in 68 dialysis sessions by means of the optical measurement of hematocrit changes corresponded very well with changes in laboratory erythrocyte counts (r = 0.90, p < 0.001) and hematocrit (r = 0.85, p < 0.001) of control blood samples drawn hourly from the arterial blood line. Hematocrit was similar in the two groups (Table 3).
SV decreased more severely in the hypotensive group (H -21.1% vs. non-H -10.8%, p = 0.04). However, heart rate tended to increase more in hypotension-prone patients (H +13.1% vs. non-H +5.7%, *P* = 0.07), resulting in a similar decrease in CO in both groups. No correlation was found between changes in CO and changes in MAP (H: r = 0.20, p = 0.35; non-H: r = 0.14, p = 0.37).

DISCUSSION

The origin of hypotension in dialysis patients is multifactorial. Some factors are patient-specific such as comorbidity of the vascular system, heart disease, autonomic neuropathy, anemia and plasma refill capacity, and some are dialysis-specific such as dialysate temperature, dialysate sodium and dialysate buffer. Ultrafiltration rate, type of membrane and eating during dialysis also are of influence. Hypovolemia is generally thought to play an important role in intradialytic hypotension since hypotension only rarely occurs without hypovolemia. However, with adequate compensation of the cardiovascular system moderate hypovolemia should not progress to symptomatic hypotension. This suggests that in hypotensive episodes the compensatory response to hypovolemia is inadequate. Important compensatory factors are CO and SVR. We found intradialytic hypotensions to occur during a deep fall in SVR with a concomitant increase in heart rate. Although less pronounced, CO and BV in the hypotensive group also decreased more than in the stable group. Factors influencing cardiac compensation are intrinsic cardiac characteristics, preload, and afterload.
Concerning the intrinsic cardiac factors, decreased contractility due to pre-existent cardiac morbidity and, even more important, decreased left ventricular compliance as a result of increased heart mass, are risk factors for hypotension in dialysis patients. Left ventricular hypertrophy (LVH) is present in more than 60% of ESRD patients (18).

Concerning the preload, several mechanisms can interfere with adequate preservation of venous return. First, possible structural abnormalities of the venous wall have been mentioned by Kooman et al. in hypertensive HD patients (19). The hereby-reduced compliance impairs plasma refill by altering capillary Starling equilibrium. Second, a *fall* in SVR, as is observed during dialysis, can reduce the venous return by interference with the DeJager-Krogh phenomenon, acting as follows (20). Normally, under conditions of *increased* SVR the flow of blood into a capillary bed will be diminished and distending pressure will thus be reduced. Consequently, because of passive recoil of the vascular bed, blood sequestered in the venous bed will be mobilized. As a result, venous return will be stimulated while cardiac afterload has increased, mitigating the fall in CO. In case of a decrease in SVR active venoconstriction reduces and venous return will be diminished (21).
Concerning the afterload of the heart, SVR is supposed to increase under conditions of hypovolemia in order to maintain adequate blood pressure. From our results it has become clear that at the moment of hypotension the SVR has fallen dramatically. The differences between *H* and *non-H* in dCO and dBV can be explained as follows. A fall in SVR at the moment of hypotension counteracts the above-mentioned DeJager-Krogh phenomenon. Therefore, venous return will fall more severely and, consequently, CO will show a more pronounced decrease. Furthermore, when SVR decreases, capillary inflow will increase resulting in a rise in intracapillary pressure. This impairs plasma refill from the interstitium and thus leads to a greater decline in BV.
Another explanation for the sudden decrease in SVR could be an imbalance between various vaso-active substances. Normally, to maintain an adequate blood pressure, an UF-induced decrease in BV will be counteracted by a rise in vasoconstrictive agents - such as (nor)adrenaline, renine and vasopressin - and/or a decrease in vasodilating agents such as nitric oxide (NO) and calcitonin-gene related peptide (C-GRP). In the past decade, several reports have been published with regard to the vaso-active response to hemodynamic changes. However, their results remain conflicting, although the role of NO as an inappropriate vasodilatator gains increasingly more evidence (6,22,23). The mechanism driving this NO release remains to be elucidated.
Santoro and coworkers distinguished a bradycardiac and a tachycardiac collapse during HD: the bradycardiac type presenting with a decrease in heart rate and an increase in stroke volume during the hypotensive episode, and the tachycardiac type with an elevation in heart rate and a reduction in stroke volume (24). Bradycardia is believed to occur due to extreme hypovolemia inducing a cardioprotective reflex, the Bezold-Jarisch reflex. This type of hypotension is therefore due to underhydration and can be reversed by adjusting the patient's dry weight. In our population no bradycardiac hypotensions occurred. Zoccali et al. recently stated that bradycardiac hypotension is the result of a more severe degree of volume depletion and that tachycardiac hypotensions predominate by far the bradycardiac hypotensions (25). As a result of increasing age and comorbidity of the dialysis population over the years, the origin of intradialytic complications such as hypotension becomes more complex by failure of multiple compensation mechanisms. The relatively 'simple' hypovolemic hypotension is observed less frequently because of adequate intervention and prevention, and becomes increasingly overruled by hypotensions of more complex origin. The challenge for the future will be to identify the specific underlying problem(s) in the individual patient and to use this knowledge for individual dialysis policy. Although several hypotheses have been raised over the years, we want to add strength to the suggestion that a fall in SVR plays a cru-

cial role in the occurrence of intradialytic hypotension, at least in a substantial group of patients. Further research will be necessary to disentangle the cause of this unfavorable fall in SVR.
We conclude that a failure to increase SVR as a response to ultrafiltration-induced hypovolemia is the most prominent cause of intradialytic hypotension. The UF-induced decrease in BV lowers blood pressure in all dialysis patients, but the degree of hypovolemia seems not to play a key role in the origin of acute, intradialytic hypotensive episodes. Since all mentioned variables could be determined non-invasively, monitoring during hemodialysis offers the possibility to identify the site of hemodynamic failure in an individual patient and thus enables proper interventions and possible prevention of dialysis-induced hypotension.

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3

A new classification of intradialytic hypotension

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submitted

ABSTRACT

Background. Intradialytic hypotension (IDH) in hemodialysis patients is a multifactorial problem. This suggests a possible classification into different types of hypotension, which could be helpful to identify different pathways leading to this complication and, consequently, to apply appropriate preventive strategies.

Methods. During hemodialysis, cardiac performance was monitored in 23 hypotensive hemodialysis patients by means of electrical impedance cardiography. Variation in blood volume was measured by means of an on-line optical probe, and hydration state by means of body impedance analysis. Based on intradialytic hemodynamic parameters an attempt was made to differentiate in the origin of IDH between the hypotensive patients.

Results. Based on the most pronounced decrease in either cardiac stroke volume or systemic vascular resistance on the moment of IDH, two groups could be differentiated. Twelve patients showed a predominant fall in systemic vascular resistance (SVR-H), whereas 11 patients showed a more pronounced decrease in cardiac output, more specifically caused by decline in cardiac stroke volume (SV-H; -38.7 ± 3.0% vs. SVR-H: -8.0 ± 4.8%, $p < 0.001$). The decrease in blood volume was not significantly different between the groups (-10.9 ± 1.6% vs. SVR-H: -7.4 ± 1.8%, $p = 0.15$). Also, no correlation was observed between decrease in blood volume and the drop in mean arterial pressure (dMAP). The correlations between dSV and dMAP ($r = 0.66$, $p = 0.03$) and change in cardiac output (dCO) and dMAP ($r = 0.83$, $p = 0.002$) were significant.
In the SVR-H group, the hypotension was due to a steep fall in systemic vascular resistance, beginning already early in HD (-32.6 ± 4.6% vs. SV-H +2.0 ± 3.1%, $p<0.001$), independent of vascular refill and cardiac function. Despite a larger UF volume, the SVR-H group demonstrated similar changes in BV and CO as the non-H group.

Conclusion. Based on different hemodynamic response patterns, IDH seems to be due to a cardiac filling failure triggered by mild underhydration leading to hypovolemia in one subgroup, while in another subgroup a fall in SVR, independent of adequate vascular refilling and cardiac function, is the cause of IDH. Different preventive strategies could be proposed for the different subgroups. Thus, a classification in stoke volume dependent and systemic vascular resistance dependent is possible within hypotension prone hemodialysis patients.

INTRODUCTION

The dialysis population has changed over the years. At present, patients on hemodialysis become increasingly older and have more comorbidity, especially of the cardiovascular system. Despite technical improvements, intradialytic hypotension (IDH) continues to be a major problem in hemodialysis treatment today. Nowadays the 'classical' hypotension, due to severe hypovolemia induced by an inappropriately assessed dry weight or a too vigorous ultrafiltration (UF) rate for the individual patient, is less frequently seen. This can be attributed to the introduction of on-line blood volume monitors, as well as to improved and extended tools to determine more accurately a patient's dry weight.
Several hypotheses concerning the origin of IDH have been raised over the years. Most of them focus on a single part of the hemodynamic regulating system. Some authors suggested that the reduced capacity of the heart to increase contractility plays an important role (1). Others blamed a sudden fall in systemic vascular resistance (SVR) as the predominant failing compensating mechanism to the decrease in mean arterial pressure (MAP) (2). In an earlier study, we reported the importance of the role of the systemic vascular resistance in the total group of hypotension prone patients (3). Recently, these findings were confirmed in a study using lower body negative pressure (LBNP). The lack of increase in SVR was more pronounced during HD than during LBNP, with cardiac filling being reduced in both situations. Concluded was that hypotension resulted from the inability to adequately increase arteriolar tone and a reduction in left ventricular function, without a significant role for relative blood volume (4). The cause of impaired vascular resistance responsiveness has been sought in sympathetic inhibition (5,6), vasoactive substances such as nitric oxide (2,7) and adenosine (8), as well as increase in body temperature during HD (9). Various preventive strategies have been proposed, such as cool dialysate (10), sodium profiling (11-13), and sympathetic agonists such as midodrine (14,15). However, these strategies have been applied to all hypotension prone dialysis patients, regardless of their individual underlying causative mechanisms. Modern patient care tends towards tailor-made, individual policies. Regarding the long history of studies on intradialytic hypotension, individualized care will likely be the future for hypotension prone dialysis patients. Some technical developments have reached the goal of modification of hemodialysis strategies by adjusting sodium content of the dialysate in response to alterations in blood volume (16).
It is clear that no simple, uniform solution can be found for such a multifactorial problem as IDH. Therefore, it is important to classify the different types of IDH. Previous classifications, such as the division into the bradycardiac and tachycardiac types, have proven their usefulness (17). The bradycardiac type was recognized to be due to a sympatho-inhibitory, cardioprotective reflex (the Bezold-Jarisch reflex), induced under conditions of extreme hypovolemia (18). These patients were likely to be underhydrated and the simple solution should be to adjust their dry weight (19).
Current techniques, such as electrical impedance cardiography, provide the opportunity to monitor intradialytic hemodynamics. Although not widespread used, it could be of great value to the physician to identify the underlying problem of the unstable patient. We studied our population of dialysis patients. The patients suffering from intradialytic hypotension were identified and subsequently subdivided based on the primary cause of their hypotension, being either due to a drop in stroke volume or due to a fall in systemic vascular resistance. Both groups were then compared to each other as well as to the stable control group (non-H). The aim of the study was to establish a new classification of IDH, based on the core blood pressure determinants.

SUBJECTS AND METHODS

Subjects

Sixty-seven patients on chronic intermittent hemodialysis were monitored during a standard hemodialysis session. Patients with documented heart failure were excluded from the study. The patients experiencing a hypotensive episode during HD were analyzed with respect to their hemodynamic response prior to the blood pressure decline. Specific emphasis was placed on the type of response, i.e. predominantly cardiac or vascular resistance. Stable patients were used as the control group. A hypotensive episode during dialysis was defined as a symptomatic decrease in systolic blood pressure of 30 mmHg or more. All patients were dialyzed three times per week for 3-5 hours with biocompatible polysulfone membranes, using bicarbonate as buffer and heparin as anticoagulant. Blood flow varied from 200 to 300 ml/min, whereas the dialysate flow was 500 ml/min and the dialysate sodium concentration 141 mmol/L. Dry body weight was determined individually by the attending physician on clinical grounds such as blood pressure, central venous pressure, and the absence of peripheral and/or pulmonary edema. Ultrafiltration volume was based on the difference between pre-dialysis and desired dry weight. Antihypertensive medication was withheld on the day of dialysis. All patients gave their informed consent.

Table 1. *Characteristics of the two hypotension groups and the control group (non-H).*

	non-H	SVR-H	SV-H
Number	44	12	11
Sex (f:m)	19:25	6:6	4:7
Age (years)	54 ± 3	62 ± 4	56 ± 5
Dry weight (kg)	63 ± 2	69 ± 3	69 ± 6
Antihypertensive Drugs	25/44	9/12	8/11
History of HD (months)	58 ± 9	27 ± 9	46 ± 13

All values are expressed as their mean ± SEM. HD = hemodialysis.

Hemodynamic variables

Blood pressure was recorded using an automatic cuff sphygmomanometer every 30 minutes and on occurrence of symptoms of hypotension, such as dizziness, muscle cramps, perspiration, or frequent yawning. Variation in blood volume (BV) was monitored by means of an on-line optical device (Critline®, In-Line Diagnostics, Riverdale (Utah), USA). This procedure is based on the non-invasive and continuous measurement of changes in hematocrit, inversely correlated to blood volume variation (20). Laboratory erythrocyte counts were performed on blood samples drawn hourly from the arterial line as control determinations of the BV monitoring. SV recordings were performed hourly utilising electrical impedance cardiography (IPG-104 impedance Mini-Lab by RJL Systems, Detroit, USA, and Equip Medikey, Gouda, The Netherlands), a valid, non-invasive, bed-side method to determine SV based on intrathoracical changes in electrical resistance due to heart pumping (21-24). Simultaneous ECG recordings provided heart rate (HR), and CO was calculated as SV * HR. In addition, SVR was obtained using the

formula SVR = MAP / CO * 80, expressed as dynes/s/cm^{-5}. Total body water (TBW) and extracellular water (ECW) were assessed at the start and the end of treatment by means of the whole body impedance method according to Lukaski (25).

Statistical analysis

Differences between several groups were analyzed by means of analysis of variance, after which differences between two specific groups were analyzed using the unpaired Student's *t* test. The relationship between different variables was evaluated using linear regression analysis. Interdependency between variables was tested by multiple regression analysis. *P* values < 0.05 were considered significant.

RESULTS

Hypotensive episodes occurred in 23 of 67 HD sessions (34%). Hemodynamic responses were analyzed and the group of hypotensive patients could be subdivided based on the most pronounced decrease in either stroke volume or systemic vascular resistance. Thus, three groups could be formed: a stable group (non-H, n = 44), a group with predominant decline in systemic vascular resistance (SVR-H, n = 12), and a group with a predominant decrease in stroke volume (SV-H, n = 11). Patient characteristics of the three groups are given in Table 1. The hypotension episodes occurred on average at 196 ± 47 minutes after initiation of HD in the SV-H group and at 206 ± 36 min. in the SVR-H group (see Figure 1). The hemodynamic variables were compared with the data measured at 180 min. in the stable control group. In the SV-H group the decrease in blood volume was significantly higher than in non-H, also after correction for a higher UF volume (see Tables 2 & 3). No significant differences were observed between the three groups in tissue hydration status (see Table 2). SV fell highly significant in the SV-H group (-38.7 ± 3.0%) but only slightly in the SVR-H (-8.0 ± 4.8%) and the non-H (-10.8 ± 3.0%) groups (see Figure 2). Multiple regression analysis in the SV-H group revealed a predominant relationship between dCO and dMAP (ß = 1.07, p < 0.001). With Pearson's correlation coefficient, the decrease in SV correlated moderately with the decrease in MAP (r = 0.66, p = 0.03), but dCO showed a strongly significant correlation with dMAP (r = 0.83, p = 0.002). No correlation was found between dSVR and dMAP. Remarkably, no correlation was found between dBV and dMAP either.

In the SVR-H group, the cumulative UF volume at the moment of hypotension was similar to the SV-H group but significantly larger than in the stable patients (Table 2). However, dBV as well as dBV/UF were similar to the non-H group, indicating adequate vascular refill. The stability of SV and CO was at least as good as in the stable group (Table 3). Besides the dMAP, the only variable significantly differing from non-H was the dSVR, which demonstrated a steep fall during the entire dialysis. As can be read from Figure 3, already after the first hour dSVR had declined more than in the non-H group (-8.8 ± 7.2% vs. +3.3 ± 2.6%, p = 0.06), and in the SV-H group (+13.4 ± 6.9, p = 0.04). This difference progressed in the subsequent hours until a measured maximum dSVR at the moment of hypotension, reaching -32.6 ± 4.6% versus +2.0 ± 3.1% in the SV-H group (p < 0.001), and +6.2 ± 3.5% in the non-H group (p < 0.001). dSVR showed a strong correlation with dMAP with multiple regression analysis (ß = 1.15, p < 0.001), as well as with Pearson's coefficient (r = 0.83, p = 0.001). The dMAP in the SVR-H group showed no correlation with either dSV or dCO.

DISCUSSION

In the present study an attempt was made to classify a group of hypotensive patients based on the main hemodynamic variables determining blood pressure, namely SV and SVR. In doing so, we observed that despite the larger UF volume in both hypotensive groups compared to stable patients, only the SV-H group demonstrated a significantly greater dBV than the non-H group. This suggests a cardiac filling problem. However, dBV appeared not to be a statistically significant determinant of blood pressure preservation, while dSV was. Adequate tachycardia could not preserve CO. For the SV-H group, it can be concluded that cardiac compensation to subclinical hypovolemia failed. Management of this type of IDH might be a slight adjustment of the patient's dry weight or cardiotonic medication.
In the SVR-H group, refilling and cardiac compensation were adequate, but SVR decreased inappropriately. The cause of this fall could not be clarified from our data. Because of the observed tachycardia and the absence of underhydration, the SVR drop could not be due to the Bezold-Jarisch reflex, a strong sympatho-inhibitory reflex originating from a deformed ventricle wall under conditions of severe hypovolemia and resulting in a strong bradycardia and peripheral vasodilatation. The presently most likely hypotheses to explain this drop in SVR are either a decrease in sympathetic tonus during HD (5,26), and/or NO release (2).
In conclusion, in the SV-dependent hypotension, mild hypovolemia seems to trigger a profound decrease in SV, probably by impaired cardiac filling, which might be prevented by dry weight adjustment. In the SVR-dependent hypotension, severe inappropriate vasodilatation is the cause of IDH. Classification of intradialytic hypotension by means of non-invasive hemodynamic monitoring enables a more specific approach of this complex, multifactorial problem, and increases insight in the different pathophysiological pathways leading to it.

Table 2. *Absolute values of hemodynamic variables at the start and at the hypotensive episode (H) or at the corresponding moment (3 h.) in the two hypotensive groups (SVR-H and SV-H) and in the control group (non-H).*

	non-H		*SVR-H*		*SV-H*	
	start	3 h.	start	H	start	H
MAP (mmHg)	102 ± 2.2	96 ± 2.2	95 ± 3	64 ± 3*	97 ± 3	70 ± 4*
CO (l)	4.6 ± 0.3	4.2 ± 0.3	3.6 ± 0.4	3.7 ± 0.4	4.5 ± 0.7	3.1 ± 0.5
SV (ml)	62.9 ± 3.8	56.1 ± 3.7	51 ± 6	46 ± 6	61 ± 10	37 ± 6$^{\#}$
HR (bpm)	73 ± 1.6	76 ± 1.6	75 ± 5	84 ± 5	75 ± 3	87 ± 3$^{\#}$
SVR (§)	2152 ±164	2282 ±213	2365 ±241	1618 ±247	2157 ±321	2178 ±332
Ht (%)	33.5 ± 0.6	35.7 ± 0.7	33.9 ± 1.4	36.9 ± 1.5	35.3 ± 1.1	39.7 ± 1.2*
UF (l)	0	2.1 ± 0.1	0	2.8 ± 0.3$^{\#}$	0	2.9 ± 0.3$^{\#}$
ECW/TBW (%)	50.9 ± 2.0	48.4 ± 2.0$^{\$}$	53.7 ± 3.4	48.5 ± 2.0$^{\$}$	46.3 ± 2.0	44.0 ± 2.0$^{\$}$

All values are expressed as their mean ± SEM. § = dynes/s/cm^{-5}; $^{\$}$ = at the end of HD;
** = P < 0.001 compared to non-H; $^{\#}$ = P < 0.05 compared to non-H.*

Table 3. *Changes in hemodynamic variables in the control group (non-H) and the two hypotension groups (SVR-H and SV-H) from the start of treatment until the average time of hypotension (or the similar moment in the non-H group).*

	Non-H	SVR-H	SV-H
dMAP (%)	-4.8 ± 1.6	-31.9 ± 4.1*	-28.2 ± 3.6*
dSVR (%)	+6.2 ± 3.5	-32.6 ± 4.6*	+2.0 ± 3.1[1]
dSV (%)	-10.8 ± 3.0	-8.0 ± 4.8	-38.7 ± 3.0*,[1]
dHR (%)	+5.7 ± 2.5	+12.9 ± 4.2	+16.0 ± 4.0
dCO (%)	-7.3 ± 2.7	+2.6 ± 4.4	-29.2 ± 3.9*,[1]
dBV (%)	-6.5 ± 0.8	-7.4 ± 1.8	-10.9 ± [#]
dBV/UF (%/l)	-2.7 ± 0.3	-2.5 ± 0.7	-4.0 ± 0.5[#]

*All values are expressed as their mean ± SEM. * = P < 0.001 compared to control group; [#] = P < 0.05 compared to control group. [1] = P < 0.001 between SVR-H and SV-H.*

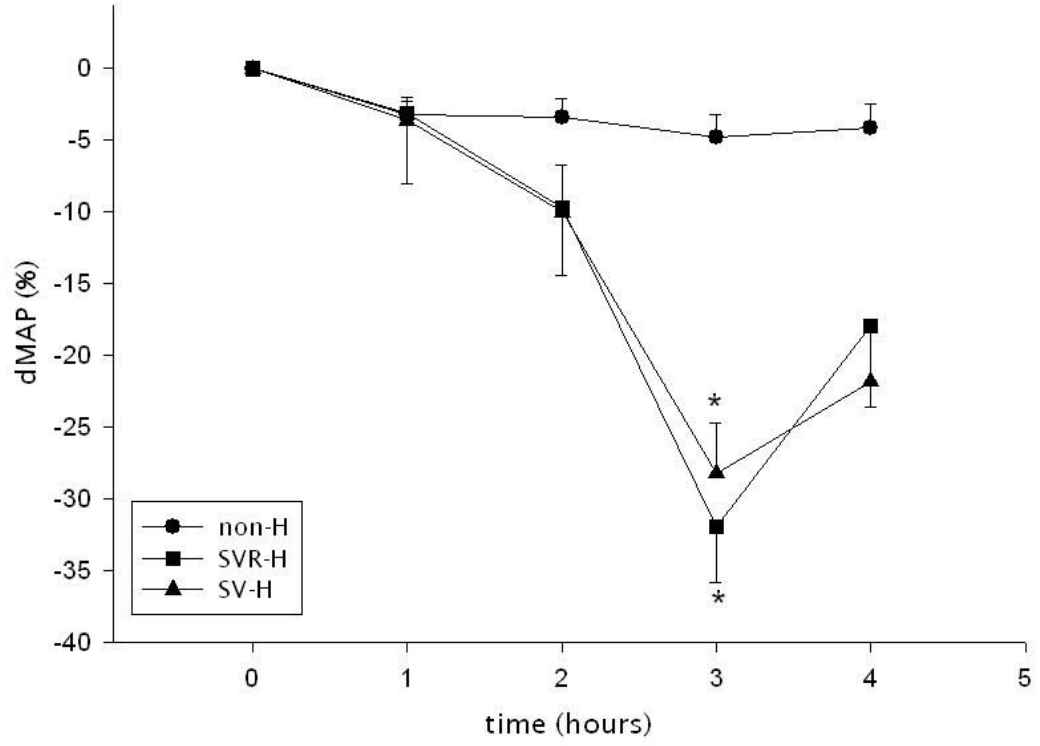

Figure 1. *The change in blood pressure during dialysis in the two hypotensive groups (SV-H and SVR-H) and the stable controls (non-H). * = p < 0.001 compared to non-H.*

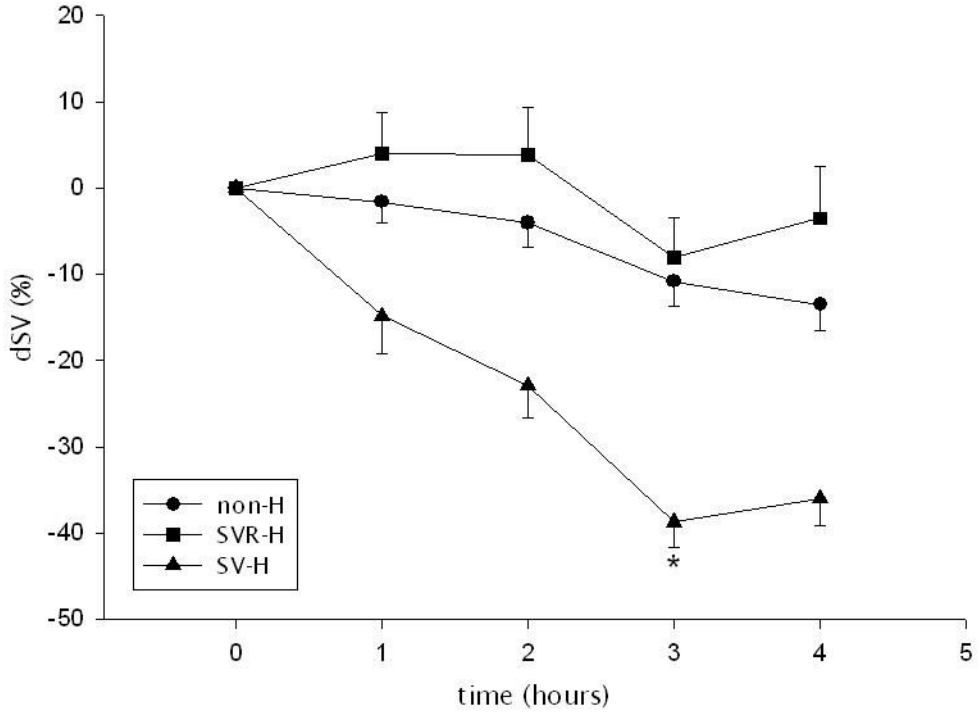

Figure 2. *The change in stroke volume during dialysis in the two hypotensive groups (SV-H and SVR-H) and the stable controls (non-H). * = p < 0.001 compared to SVR-H and non-H.*

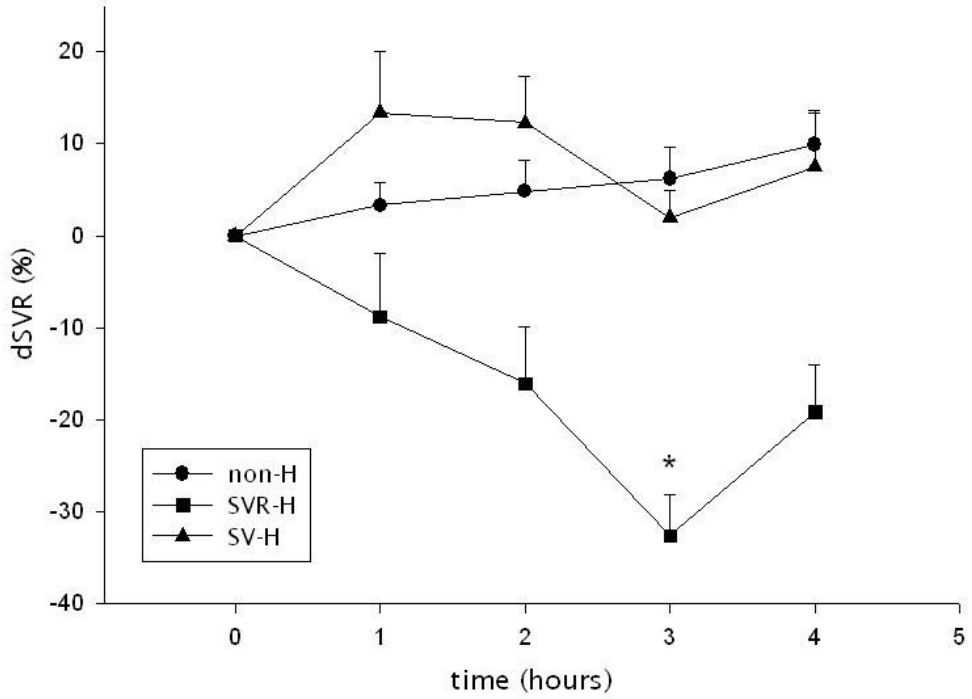

Figure 3. *The change in systemic vascular resistance during dialysis in the two hypotensive groups and the stable controls (non-H). * = p < 0.001 compared to SV-H and non-H.*

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4

Clinical reproducibility of intradialytic hypotension characteristics

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submitted

ABSTRACT

Background. Intradialytic hypotension is of multifactorial origin, several strategies being developed to prevent it. In order to customize hemodialysis care, it is important to classify different types of intradialytic hypotension. In a previous study we classified hypotension prone hemodialysis patients into two groups based on a fall in systemic vascular resistance or a fall in stroke volume. In the present study repeated measurements of intradialytic hemodynamics were performed in hypotension prone patients, aimed at demonstrating reproducibility of category of intradialytic hypotension.

Methods. Ten hypotension prone hemodialysis patients were monitored hemodynamically during five dialysis sessions. Noninvasive bedside Electrical Impedance Cardiography provided hemodynamic variables such as stroke volume, cardiac output and systemic vascular resistance.

Results. In 36 out of 50 sessions a hypotensive episode occurred. In 7 out of 10 patients the hemodynamic response pattern was reproducible, whereas in the remaining three patients the pattern was unpredictable.

Conclusion. Hemodynamic monitoring during hemodialysis provides important information about type of intradialytic hypotension. In the majority of dialysis patients the origin of hypotension is reproducible. This enables application of specific individualized therapy.

INTRODUCTION

Intradialytic hypotension (IDH) occurs when normal compensatory mechanisms cannot keep up with the removal of fluid and solutes in a short time span. The main factor is the reduction of blood volume, necessitating adequate capillary refill to maintain blood pressure. Normal compensatory mechanisms include increase in heart frequency and contractility to maintain cardiac output during hypovolemia. Furthermore, arteriolar constriction increases afterload and venoconstriction mobilizes the venous blood pool in order to increase venous return.

Failure of either of these mechanisms may lead to intradialytic hypotension, leading to diminished dialysis efficacy and discomfort for the patient.
Diminished cardiac reserve leads to a poor response to hypovolemia (1). Decreased systemic vascular resistance plays an important role in inducing hypotension (2), its possible mechanisms being a paradoxal withdrawal of sympathetic tone (3), local release of vaso-active substances as adenosine or nitric oxide, or a decreased autonomic response (4-6).
Finally, impaired venous tone leads to diminished capillary refill, thereby reducing venous return, resulting in a diminished cardiac filling. Ultimately, a fall in blood pressure will occur (7).
Several strategies have been proposed to support compensatory mechanisms. There are strategies to enhance capillary refill by reducing osmotic shifts such as balanced sodium profiling (8). Furthermore, lower temperature dialysis improves venous tone and thereby venous return (9-11). Some authors reported beneficial effects of sympathetic agonists such as midodrine to counteract sympathetic withdrawal (12).
However, all preventive strategies may have side effects. Sodium profiling, especially when administered incorrectly, may cause hypertension by sodium loading. Cool dialysate dialysis and sympathetic agents may be uncomfortable for the dialysis patient.
This raises a need for determination of individually effective preventive strategies, based on the pathophysiologic mechanism leading to hypotension. Electrical impedance cardiography provides a tool for noninvasive monitoring of intradialytic hemodynamics (13-16) and might therefore be helpful to reach this goal.

In a previous study we could classify hypotension prone patients into two categories, based on a predominant decrease in either systemic vascular resistance (SVR) or stroke volume (SV) (submitted data). The present study is aimed at investigating whether these different pathophysiologic pathways are reproducible within hypotension prone hemodialysis patients, by means of monitoring several dialysis sessions.

PATIENTS AND METHODS

Patients

Ten hypotension prone patients were studied during 5 hemodialysis sessions. Hypotension prone was defined as having had more than three hypotensive episodes during the ten prior consecutive dialysis sessions. A hypotensive episode during dialysis was defined as a decrease in systolic blood pressure of >30 mmHg or an absolute systolic blood pressure of < 90 mmHg during dialysis, accompanied by hypotensive symptoms such as dizziness, frequent yawning or perspiration. Patient characteristics are given in Table 1.
No interventions such as change in dry weight occurred during the study period. Indi-

vidual hemodynamic responses to simultaneous ultrafiltration and solute dialysis were monitored. All patients were dialyzed three times per week for 4 hours with biocompatible polysulfone membranes, using bicarbonate as buffer and heparin as anticoagulant. Blood flow was 250 ml/min, whereas the dialysate flow was 500 ml/min and the dialysate sodium concentration 140 mmol/L. Ultrafiltration volume was based on the difference between pre-dialysis and desired dry weight. All patients gave their informed consent.

Table 1. *Patient characteristics*

Patient	Age (yrs)	Sex	Duration of HD (months)	Dry weight (kg)	Antihypertensive drugs (no.)
A	37	M	72	57.5	4
B	70	F	12	46.5	3
C	51	M	30	111.5	1
D	57	F	125	54	0
E	60	F	66	72	1
F	78	M	8	79.5	0
G	31	M	31	57.5	2
H	40	F	5	75	1
I	67	M	40	81.5	0
J	57	M	14	125	4

Methods

Blood pressure was recorded using an automatic cuff sphygmomanometer every 30 minutes and on occurrence of symptoms of hypotension, such as dizziness, muscle cramps, perspiration, or frequent yawning. Blood volume variation was monitored by means of an on-line optical device (Critline®, In-Line Diagnostics, Riverdale (Utah), USA), based on the non-invasive and continuous measurement of changes in hematocrit, inversely correlated to blood volume (BV) variation (17,18). Laboratory erythrocyte counts were performed on blood samples drawn hourly from the arterial line as control determinations of the BV monitoring. Stroke volume (SV) recordings were performed hourly utilising electrical impedance cardiography (IPG-104 impedance Mini-Lab by RJL Systems, Detroit, USA, and Equip Medikey, Gouda, The Netherlands), a valid, non-invasive, bed-side method to determine SV based on intrathoracical changes in electrical resistance due to heart pumping (13,14,19,20). Simultaneous ECG recordings provided heart rate (HR), and cardiac output (CO) was calculated as SV * HR. In addition, systemic vascular resistance (SVR) was obtained using the formula SVR = (MAP / CO) * 80, expressed as dynes/s/cm^{-5} where MAP is mean arterial pressure (mmHg).

Statistical analysis

The patterns of hemodynamic response were shown in a descriptive manner. Differences between groups were analysed by means of unpaired Students' T-tests. Correlation coefficients were calculated according to Pearson.

RESULTS

In 50 hemodialysis sessions in 10 hypotension prone patients, 36 dialysis-induced hypotensions requiring intervention occurred (72%).
27 of 36 IDH episodes could be attributed to a predominant decrease in either SV (n=18) or SVR (n=9). The remaining 9 hypotensions were a combination of both.
In the group of hypotensive dialysis sessions due to a decrease in SV (SV-H group), the only factor significantly correlated to MAP was SV ($r = 0.78$, $p = 0.04$). SVR did not influence MAP in that group. In the group of hypotensive sessions due to a fall in SVR (SVR-H group), however, SVR was the only correlated determinant of MAP ($r = 0.73$, $p = 0.05$), whereas there was no significant influence of SV. Interestingly, in the combination-group there also was a significant role for SVR ($r = 0.78$, $p = 0.01$), whereas MAP did not correlate with SV ($r = 0.47$, NS), or with BV ($r = 0.18$, NS). The influence of BV on MAP was limited as there was no significant correlation in any subpopulation between BV and MAP or between BV and SV.
A recognisable pattern was observed in 6 out of 10 patients, as is shown in Table 2. Four patients (A,B,D,F) became repeatedly hypotensive due to a predominant fall in stroke volume (SV) despite peripheral vasoconstriction, shown as an increase in SVR. The hemodynamic response of IDH characterised by a decrease in SV without an adequate SVR increase is shown in Figure 1. Two patients (G,H) showed a pattern of decrease in SVR over several hypotensive episodes with only minimal decrease or even increase in SV, except once (H1). Figure 2 displays an example of such a hemodynamic response. One patient (C) showed during 5 hemodialysis sessions only one hypotensive episode due to a diminished SV with only minimal SVR increase, whereas in the four stable sessions SVR response was adequate.
However, 3 patients (E,I,J) failed to show a recognisable pattern, with absence of cardiac reserve capacity and absence of adequate vascular response.

Measured by clinical behaviour and expressed in hemodynamic response, reproducibility was strong in 7 out of 10 patients.

DISCUSSION

Cardiovascular disease is the leading cause of morbidity and mortality in ESRD patients (21,22). Factors contributing to cardiovascular dysfunction are various (23,24). Pre-existing diseases as diabetes mellitus are playing an important role (25), as well as diminished autonomic function in uremia (26). IDH has been shown to increase mortality as an independent factor (27). Insight in individual hemodynamic response patterns provides opportunities to develop and modify preventive and intervention strategies, thereby minimizing adverse effects on fluid and solute removal as well as discomfort due to these strategies. In our study group, 70% of hypotension prone patients could be identified as having a reproducible hemodynamic response. In the remaining - combination -patients, alternating stroke volume and vascular resistance decrease caused the intradialytic hypotension. In this group there was a significant correlation between SVR and MAP, without a significant role for SV, resembling the pattern observed in the SVR-H group. It is hypothesized that paradoxical SVR decrease is the main cause of intradialytic hypotension, except in a group of patients where vascular compliance is diminished to an extent that even slight changes in intravascular volume may lead to stroke

Table 2. *Change in hemodynamic parameters during hemodialysis, from start of dialysis until moment of hypotension or equivalent.*

Patient	dMAP	dSVR	dSV	DBV	UF	IDH
A1	-29	-4	-35	-6	2,1	SV
A2	-13	-17	-6	-7	1,5	-
A3	0	38	-24	-3	2,8	-
A4	-11	-17	0	-8	2,8	-
A5	-15	-2	-12	-5	2,7	SV
B1	-33	6	-52	-12	3,5	SV
B2	-29	7	-52	-14	2,6	SV
B3	-32	-19	-33	-13	2,9	SV
B4	-28	10	-53	-11	2,8	SV
B5	-7	-21	-8	-13	3,3	-
C1	8	60	-40	-17	5,6	-
C2	3	-2	-19	-13	4,8	-
C3	-9	25	-28	-14	5,2	-
C4	-19	13	-57	-6	3,9	SV
C5	15	62	-36	-10	4,8	-
D1	-24	28	-38	-6	1,9	SV
D2	-16	54	-55	-6	2,0	SV
D3	-48	-8	-43	-9	2,0	SV
D4	-53	3	-60	-13	2,8	SV
D5	-46	28	-56	-6	1,7	SV
E1	-10	17	-36	-9	3,6	-
E2	-24	17	-43	-13	3,5	SV
E3	-16	-50	30	-5	2,8	SVR
E4	-26	-26	-19	-7	2,6	Combi
E5	-11	-5	-15	-11	3,6	-
F1	-28	-13	-25	-18	4,3	Combi
F2	-33	1	-44	-19	4,5	SV
F3	-21	-11	-13	-17	4,2	Combi
F4	4	33	-31	-15	4,4	-
F5	5	-9	6	-6	3,3	-
G1	-46	-42	-11	-13	3,1	SVR
G2	-42	-49	3	-14	3,1	SVR
G3	-29	-36	-3	-6	2,4	SVR
G4	-7	-18	1	-12	3,2	-
G5	-18	-41	2	-17	3,2	SVR
H1	-18	8	-34	-2	3,5	SV
H2	-33	-51	8	-7	2,9	SVR
H3	-21	-40	13	-7	2,9	SVR
H4	-18	-48	42	-3	1,8	SVR
H5	-19	-15	-18	-6	2,9	-
I1	-33	3	-42	-7	1,9	SV
I2	-45	-23	-25	-7	1,9	Combi
I3	-41	-26	-18	-4	2,8	Combi
I4	-30	13	-45	-5	2,5	SV
I5	-27	-11	-18	-4	2,7	Combi
J1	-51	-36	-32	-15	4,7	Combi
J2	-30	-11	-31	-13	4,1	Combi
J3	-25	12	-38	-12	5,1	SV
J4	-52	-57	11	-8	4,7	SVR
J5	-34	-4	-38	-11	4,9	SV

dMAP/SVR/SV/BV are changes in the different hemodynamic variables (%). IDH = type of intradialytic hypotension; stroke volume or systemic vascular resistance determined, or a combination of both. '–' = no hypotension occurred.

volume decrease inducing hypotension. The group of patients with intradialytic hypotension without a recognisable pattern could be in a process where progressive vascular dysfunction overrules primary vascular resistance decrease as the cause of hypotension.
Our data show that there appear to be two types of categories of intradialytic hypotension. The first group consists of cardiac compromised patients, with narrow margins in cardiovascular reserve capacity. Prolonged or more frequent dialysis sessions can diminish the magnitude of variation in fluid state. The second group of patients experiences a decrease in systemic vascular resistance, which is inadequate during hypovolemia. In this (younger) group preventive strategies such as cool dialysate, sodium profiling or alpha-agonists might be of benefit.
Non-invasive monitoring of hemodynamics during hemodialysis by means of electrical impedance cardiography provides an insight in intra-individual responses to hemodialysis. Since decades it is known that without ultrafiltration, intradialytic hypotension does not occur (28). Furthermore, methods such as bioelectrical impedance analysis (BIA) provide a more accurate dry weight determination (29,30). However, prediction of occurrence of IDH based on changes in hydration state during hemodialysis remains difficult (31,32). Different pathophysiologic pathways leading to IDH have been identified, followed by as many strategies to prevent it, such as physiological (hypothermia, food avoidance) and pharmalogical (alpha-agonists) methods to improve SVR, as well as methods to improve SV by increasing venous return or myocardial contractility (33). All these interventions have their disadvantages in the sense of side effects or discomfort for the patient.
We conclude that intradialytic hypotension has been thoroughly studied on a pathophysiological basis, not on an individual basis. Non-invasive, bedside monitoring devices provide the opportunity to classify the individual hypotension prone patient and to apply the most effective preventive strategy. Necessary is the intra-individual reproducibility of the cause of IDH, appearing to be clear in 70% of hemodialysis patients.

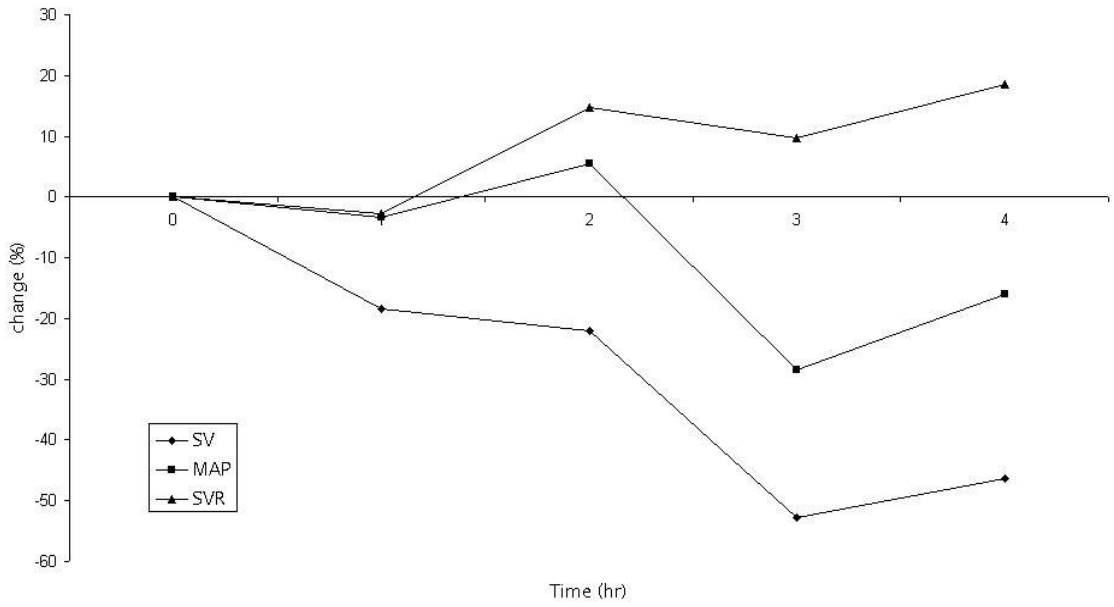

Figure 1. *Characteristic hemodynamic response during hemodialysis in stroke volume dependent hypotension, which occurred at 3 hr.*

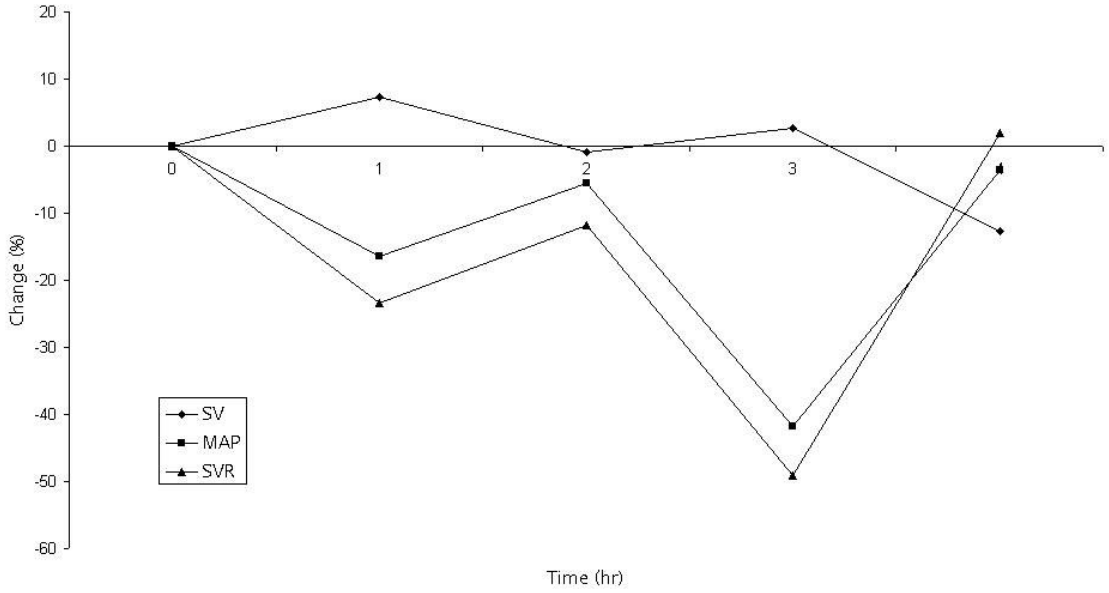

Figure 2. *Characteristic hemodynamic response during hemodialysis in vascular resistance dependent hypotension, which occurred at 3 hr.*

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5

Intradialytic hypotension in relation to pre-existent autonomic dysfunction in hemodialysis patients

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ABSTRACT.

After having monitored hemodynamics during hemodialysis, we examined autonomic nervous function in rest prior to a next dialysis session in 28 patients on chronic intermittent hemodialysis. The aim was to compare intradialytically hypotensive with stable patients to assess whether blood pressure regulating mechanisms were related to basal autonomic function, assessed as heart rate variability (HRV) tested by means of the deep breathing test, the lying-to-standing test, and the Valsalva maneuver. Impedance cardiography was used to determine stroke volume and cardiac output during dialysis. In addition, blood pressure was registered automatically and systemic vascular resistance calculated. An on-line optical device monitored blood volume variation.
Intradialytic hypotension was observed in 10 patients (36%). Systemic vascular resistance in hypotensive patients decreased considerably (-14.0 ± 5.9%), while it increased in stable patients (+9.9 ± 4.6%, $p = 0.004$). Heart rate rose significantly in hypotensive patients (11.5 ± 3.8%) in comparison to stable patients (-0.2 ± 2.8%, $p = 0.02$). However, no significant differences in autonomic function were observed between hypotensive and stable patients. Although both groups showed impaired autonomic function, no significant correlation between changes in hemodynamics during dialysis and autonomic function at rest could be ascertained.
In conclusion, hypotension during hemodialysis is not related to a patient's autonomic function at rest. This suggests that structural neuronal differences are not responsible for the severe decrease in systemic vascular resistance in intradialytic hypotension.

INTRODUCTION.

Autonomic neuropathy is a well-known complication of uremia occurring in almost all uremic patients. It is probably caused by high levels of circulating uremic toxins (1), and results in a derangement of the para- and orthosympathetic nervous system, and a reduced end organ responsiveness to catecholamines (2).
In the past, many authors have reported a dysfunction of the baroreflex arc to be one of the causes of hypotension during hemodialysis (HD) (3-5). In 1974, Kersh et al. first related intradialytic hypotension to autonomic neuropathy (6). In subsequent reports effort was made to locate the site of the dysfunction, which was concluded to be predominantly in the afferent limb of the baroreflex arc, and especially in the baroreceptors themselves (2,7).
Several other investigators, however, reported contradictory results. Zoccali et al. for instance, showed no difference in autonomic function between hypotensive and non-hypotensive patients during uremia, except for diabetic patients (8). Likewise, in other studies a causal relation between autonomic dysfunction and dialysis-induced hypotension could not be found (9-11). However, these studies did not provide further additional hemodynamic variables during HD. Recently, a diminished sympathetic response on blood volume decrease *during* HD was demonstrated in hypotension prone patients by means of spectral analysis of HRV (12-14). The sympatho-vagal balance, however, was significantly different between stable and unstable patients already at the beginning of HD, when the process of HD itself had not had any influence on autonomic function yet. This suggests that the basal autonomic function in stable and unstable patients is different.
Therefore, in the present study an attempt was made to clarify the role of the basal autonomic status in relation to changes in hemodynamics *during* HD. First, 28 patients were monitored hemodynamically during a standard HD and subsequently divided into a hypotensive and a stable group. In this dialysis session blood pressure (MAP), stroke volume (SV), heart rate (HR), cardiac output (CO), systemic vascular resistance (SVR), and blood volume (BV) were monitored. Second, we tested the cardiovascular reflex arc in the intradialytically hypotensive and the stable dialysis patients at rest prior to a next dialysis session with a standard battery of three autonomic function tests.

PATIENTS AND METHODS.

Patients.

Based on cardiovascular stability during a previously monitored dialysis session, 28 patients on chronic intermittent hemodialysis were divided into a hypotensive group (H; n = 10) and a stable group (non-H; n = 18). A hypotensive episode was defined as a sudden decrease of systolic blood pressure of more than 30 mmHg or an absolute systolic blood pressure below 90 mmHg. Based on past dialysis performance all hypotensive patients appeared to have hypotensive episodes in more than 30% of the dialysis sessions, whereas stable patients experienced symptomatic hypotension in less than 5% of the sessions.
Patient characteristics of the two groups are provided in Table 1. No significant differences in age, HD history and dry weight were present. Patients were dialyzed 9 to 15 hours per week divided over 2-3 sessions with biocompatible polysulphone membranes. Bicarbonate was used as buffer and heparin as anticoagulant. Blood flow varied from

200 to 350 ml/min, whereas the dialysate flow was 500 ml/min and the dialysate sodium concentration 141 mmol/L. Dry body weight was determined individually by the attending physician on clinical grounds such as blood pressure, central venous pressure, and the presence of peripheral and/or pulmonary edema. Ultrafiltration (UF) volume was calculated as the difference of the pre-dialysis weight and dry weight. Cardiovascular medication was withheld on dialysis days to minimize interference with intradialytic blood pressure regulation. To minimize interference of antihypertensive medication on autonomic function, the autonomic function tests were performed on a dialysis day, prior to dialysis. Complete withdrawal of antihypertensive medication for the duration of the experiments was not performed, because of the risks for the clinical status of the patients. Infusion of saline or gelatin (Gelofusin®) was used to treat hypotensive episodes. All patients gave their informed consent for participating in the studies.

Table 1. *Characteristics of the hypotension-prone (H) and the stable (non-H) patients.*

	H	non-H
Number	10	18
Sex (f:m)	5:5	5:13
Diabetes Mellitus	1/10	2/18
Antihypertensive Drugs	8/10	6/18
Age (yrs)*	45 ± 5.0	51 ± 4.2
Dry weight (kg)*	62.8 ± 2.9	67.9 ± 4.1
Body surface area (m^2)	1.70 ± 0.04	1.78 ± 0.06
History of HD (months)*	53 ± 13	83 ± 17

** Expressed as mean ± SEM. No significant differences between the two groups.*

Hemodynamic variables during dialysis.

In a dialysis session prior to the autonomic function tests every patient was monitored regarding his cardiovascular stability. Electrical impedance cardiography was performed to monitor SV at the start of dialysis and every hour thereafter using the IPG-104 impedance Mini-Lab (RJL Systems, Detroit, USA, and Equip Medikey, Gouda, The Netherlands) (15). CO was calculated from the HR obtained from an ECG and the SV. SVR was calculated according to Ohm's law, as (MAP/CO) * 80, where MAP is mean arterial pressure. The constant value 80 in the expression above makes it possible to express SVR in units: dynes/s/cm^{-5}. Variation in BV was monitored continuously by means of an optical device detecting an increase in hematocrit by the reflection of infrared light by erythrocytes (Critline®, In-Line Diagnostics, Riverdale (Utah), USA). BV was expressed in total percentage change compared to the pre-dialysis value as well as percentage change per liter of UF. Blood pressure was recorded every 30 minutes in stable condition or every 10 minutes when any symptom of a decrease in blood pressure arose, such as dizziness, muscle cramps, perspiration, or frequent yawning. The same investigator using a sphygmomanometer always performed the blood pressure measurements. Finally, total body water (TBW) was assessed by means of whole body impedance measurements at the start and at the end of the dialysis session (16).

Autonomic function tests.
A battery of three autonomic function tests based on cardiovascular reflexes was performed to gain insight in the patient's autonomic activity. These tests were 1) a deep breathing test to assess parasympathetic heart rate control, 2) a lying-to-standing test to assess both the cardiac reflex arc (sympathetic as well as parasympathetic) and peripheral vasomotor function, and 3) a Valsalva maneuver to determine both sympathetic and parasympathetic function. During these tests the variability in the length of the R-R intervals on the ECG was measured. R-R intervals were automatically obtained by a PC-based data acquisition system from a hardware QRS-detector (band-pass filtered adaptive R-wave level detection), using a bipolar chest lead. The data acquisition program precisely guided the test performance and computed the test variables as well. All tests were performed at rest just before a dialysis session. As autonomic function declines with increasing age, age-dependent reference values were applied according to Piha (17). In the latter study the expected values corrected for age were provided per test, with the lower 10 percentile as lowest normal value and the lower 2.5 percentile as the lowest borderline value. Values under the 2.5 percentile were considered abnormal. To obtain a simple measure for autonomic function, every patient was given a normal (1) or abnormal (0) qualification, according to the age-related reference values, for each of the four autonomic variables (IE-difference (bpm); Max/min ratio; HR_{max} (bpm); Valsalva Ratio) computed from the three tests (see below). The sum of the four test qualifications was defined as the *Total Autonomic Index* and considered as an overall index of autonomic function, ranging from 0 (severe dysfunction) to 4 (normal).

1) Deep breathing test.
After a period of supine rest for five minutes the patient was asked to breath deeply for one minute in a fixed rhythm of six breaths per minute. The inspiration-expiration difference (IE-value) was defined as the mean of the differences between maximum and minimum heart rate (in bpm) over the consecutive deep breaths. This test was performed twice and the average was calculated. The IE-value is almost exclusively a measure for (cardiac) parasympathetic function since rapid beat-to-beat variation of heart rate can only be mediated by the vagal nerve (18).

2) Lying-to-standing test.
Standing up from supine position produces a characteristic cardiovascular response, with significant changes in heart rate and peripheral vasoconstriction. Blood pooling in the lower part of the body provokes a decrease in blood pressure, which is counteracted instantly by a vagally mediated initial tachycardia followed by a sympathetically induced prolonged tachycardia. The maximum increase in heart rate (HR_{max}, in bpm) is, therefore, informative about the cardiac reflex arc, sympathetic as well as parasympathetic. Subsequently, a sympathetic vasomotor reflex induces peripheral vasoconstriction. The hereby increasing peripheral resistance and partly normalizing venous return result in almost complete recovery of blood pressure, and consequently in a relative bradycardia. The ratio between the maximum HR around the 15th beat after standing up and the minimum HR around the 30th beat after standing up (Max/min ratio) thus indirectly provides information about the peripheral sympathetic function (19).

3) Valsalva maneuver.
The patient in a relaxed sitting position was asked to take a full deep breath and blow into a mouthpiece connected to a manometer and to maintain an expiratory pressure of 30 mmHg for 15 seconds, and to finally expire and relax for another 45 seconds. After practicing, the maneuver was repeated twice and the obtained average variable was used. The reflex response to this maneuver consists of two phases: 1) an immediate (vagal) and sustained (sympathetic) tachycardia and peripheral vasoconstriction during strain evoked by the drop in blood pressure due to obstruction of venous return, 2) an overshoot in blood pressure after pressure release due to normalizing stroke volume ejected in a still constricted arterial system resulting in a strong immediate reflex bradycardia (vagally mediated). The ratio between the longest R-R interval within 15 seconds after release and the shortest interval during strain is defined as the Valsalva Ratio (VR) (18).

Statistical analysis.
Differences between the two groups were analyzed by means of the unpaired Student's *t* test, and between different time intervals during dialysis within one group by means of the paired Student's *t* test and the repeated measures analysis of variance, when appropriate. The relationship between different variables was evaluated using Pearson's correlation coefficient. Interdependency between variables was tested by multiple linear regression analysis. Chi square tests were performed to assess significant differences between H and non-H groups in distributions of antihypertensive medication and autonomic function scores. *P* values < 0.05 were considered significant.

RESULTS.

Hemodynamic variables during dialysis.
Intradialytic hypotension was observed in 10 patients (36%). The hypotensive episodes occurred on average after three hours of dialysis. At the moment of hypotension, *absolute* values only differed significantly in MAP (H 71 ± 5 vs. non-H 88 ± 3 mmHg, $p < 0.001$). SV and TBW tended to be higher in the stable patients, but equalized in both groups when expressed per square meter body surface area (BSA) or kilogram of body weight, respectively (see Table 2).
Multiple linear regression with *relative* values, i.e. the change of a variable from the start of dialysis until the moment of hypotension or the corresponding moment in time in the non-H group, revealed a predominant role for the change in SVR (dSVR) in the decline of MAP (dMAP) in both groups (see Table 3). Indeed, the SVR increased adequately in the stable patients (+9.9 ± 4.6%), whereas the hypotensive patients showed a marked decrease (-14.0 ± 5.9%, $p = 0.004$) (see Table 4).
No significant correlation was found between dMAP and dSV in either of the groups with simple regression analysis. However, the SV showed an almost equally important role in the decrease of MAP according to the multiple regression analysis.
There were significant differences in decrease in BV between stable and unstable patients, due to a greater UF volume in hypotensive patients (see Table 4). However, according to the multiple as well as the simple regression analysis, there was no significant influence of the dBV on blood pressure variation (see Table 3).

Table 2. *Mean hemodynamic variables (SEM) at the start and end of dialysis, and at the moment of hypotension (t_H) in group H or the corresponding moment (t_{3h}) in group non-H.*

	H			non-H		
	start	t_H	end	start	t_{3h}	end
MAP (mmHg)	95 (3.7)	71 (4.6)	76 (4.5)*	93 (2.3)	88 (2.6)[1]	88 (9.4)[2,#]
SV (ml)	56.4 (9.1)	46.0 (7.7)	43.2 (7.1)[#]	72.6 (6.6)	65.2 (6.4)	62.0 (6.4)*
SVI (ml/m^2)	33.7 (5.7)	27.3 (4.6)	25.6 (4.2)	40.8 (3.4)	36.5 (3.4)	34.7 (3.4)
HR (bpm)	73 (3.7)	81 (3.7)	81 (3.7)*	73 (2.7)	72 (2.6)	74 (2.6)
CO (l/min)	4.0 (0.6)	3.5 (0.5)	3.3 (0.5)[#]	5.2 (0.5)	4.6 (0.4)	4.5 (0.5)*
SVR (§)	2294 (321)	2032 (381)	2324 (475)	1732 (244)	1823 (217)	1914 (236)
TBW (l)	36.0 (2.3)		30.9 (2.1)*	41.0 (2.8)		34.6 (2.0)*
TBW/kg (l/kg)	0.56 (0.03)		0.50 (0.03)	0.59 (0.02)		0.52 (0.02)
UF (l)	0	2.6 (0.2)	2.9 (0.2)[#]	0	1.8 (0.1)[1]	2.4 (0.2)*

** P < 0.001 within group; [#] P < 0.05 within group; [1] P < 0.001 H compared to H; [2] P < 0.05 H compared to H. § = dynes/s/cm^{-5}*

Table 3. *Multiple regression coefficients (ß) and Pearson's correlations (r) for the relation between trends in hemodynamic variables and decrease in blood pressure (dMAP).*

	non-H (n = 18)				**H (n=10)**			
	mult. regression		***correlation dMAP***		***mult. regression***		***correlation dMAP***	
	ß	***p***	***r***	***p***	***ß***	***p***	***r***	***p***
dSVR	1.73	< 0.001	0.66	0.003	1.30	< 0.001	0.72	0.02
dSV	1.43	< 0.001	-0.15	0.56	0.97	0.001	-0.20	0.58
dHR	0.47	0.02	-0.03	0.91	0.49	0.01	0.44	0.20
dBV	-0.02	0.90	-0.19	0.46	-0.06	0.56	-0.12	0.75

Table 4. *Percentage change in hemodynamic variables (SEM) from the start of dialysis until the moment of hypotension (H) or the corresponding moment (non-H).*

	H	non-H	*P* value
MAP (%)	-25.4 (3.9)	-5.1 (2.3)	<0.001
SV (%)	-19.5 (5.5)	-10.9 (3.2)	0.16
HR (%)	11.5 (3.8)	-0.2 (2.8)	0.02
CO (%)	-11.1 (5.3)	-11.9 (2.9)	0.89
SVR (%)	-14.0 (5.9)	9.9 (4.6)	0.004
BV (%)	-10.6 (1.7)	-5.8 (0.9)	0.01
BV/UF (%/l)	-4.2 (0.6)	-3.2 (0.5)	0.22

BV/UF = blood volume per liter ultrafiltration.

Table 5. *Results of autonomic function tests (SEM) of hypotensive (H) and stable (non-H) patients. Normal (N), borderline (B) or abnormal (A) qualification is provided in number of patients.*

	H				non-H				
	mean	N	B	A	mean	N	B	A	*P* value
Deep Breathing IE (bpm)	10 (2)	5	4	1	11 (2)	11	4	3	NS
Lying-to-standing HR_{max} (bpm)	15.0 (2.0)	2	2	6	14.5 (1.6)	5	6	7	NS
Max/min	1.16 (0.04)	2	7	1	1.15 (0.03)	9	5	4	NS
Valsalva Maneuver VR	1.27 (0.05)	6	3	1	1.40 (0.08)	14	1	3	NS
Total Autonomic Index	2.30 (0.34)				2.58 (0.30)				NS

IE = inspiration - expiration difference; HR_{max} = maximum increase in heart rate after standing up; Max/min = ratio between maximum and minimum heart rate after standing up; VR = Valsalva ratio; NS = not significant.

Autonomic function tests.
No differences in responses on the autonomic tests could be demonstrated between the hypotensive and the non-hypotensive group (Table 5). When the three diabetics were excluded, the results did not change statistically, although the diabetics did have the lowest scores on all tests (data not shown). The identical basal autonomic status, expressed as HRV variables, did not show any significant correlation with variations in MAP and SVR during HD ($p > 0.1$ for all correlations, data not shown). More specifically, no correlation was found between the Max/min, a variable reflecting mainly sympathetic function, and the dSVR, principally regulated by sympathetic tonus, in group H ($r = 0.31$, $p = 0.39$), nor in group non-H ($r = -0.17$, $p = 0.51$).
The *Total Autonomic Index* averaged 2.30 ± 0.34 in the hypotensive patients, whereas the stable patients reached 2.58 ± 0.30 ($p > 0.5$). A chi square test performed on the distribution into normal and not-normal (i.e. borderline + abnormal) autonomic function showed no significant differences for the four autonomic function variables ($p > 0.2$ for all variables). All four autonomic function variables were negatively correlated with age ($p < 0.02$ for all correlations), justifying the use of age-dependent reference values.

DISCUSSION.

In our study we examined if a direct relation between intradialytic hemodynamic variables and autonomic function variables at rest could be established. The observed severe decrease in SVR in hypotensive patients, compared to the rise in SVR in stable patients required a re-evaluation of the involvement of the autonomic function in intradialytic hypotension. However, measured at rest, no difference in autonomic function was observed between stable and hypotensive patients, and no correlation with change in MAP or SVR was present. Combining direct measurements of autonomic function and intradialytic hemodynamics, this clearly demonstrates the irrelevance of the pre-existent autonomic function at rest.
Remarkably, BV appeared to have no significant influence on blood pressure, indicating that hypovolemia was not the single cause of intradialytic hypotension. Perhaps increasing age and comorbidity in the dialysis population are reasons for a more complex and multifactorial origin of the intradialytic hypotensions today. Although a decrease in SVR becomes currently more accepted as an important inductor of intradialytic hypotension, the cause for this SVR decrease remains to be clarified. Our study did not include intradialytic measurements of vasoactive substances as catecholamines and nitric oxide, which are powerful determinants of SVR. Results so far in this area are still controversial.
In an attempt to elucidate the fall in SVR during HD, some authors have claimed a role for the Bezold-Jarisch reflex (20), a mechanically induced sympatho-inhibitory reflex originating from the ventricles to protect the heart against structural damage under conditions of extremely low CO (21). Ligtenberg and colleagues even suggested that a sympathetic impulse, eliciting an adequate reaction at rest, provoked this sympatho-inhibitory reflex under conditions of low CO, as can also be seen in normals undergoing lower body negative pressure (22). However, to conclude the activity of such a reflex causing sympatho-inhibition, a relative bradycardia must be present. Therefore, Santoro et al. made a distinction between tachycardiac and bradycardiac hypotensions (23). Very recently, Zoccali et al. demonstrated that this bradycardia occurred only in up to 20% of all intradialytic hypotensive episodes and was indicative for underhydration, requiring

adjustment of the patient's dry weight (24). In our population no bradycardia occurred during hypotensive episodes, suggesting a different process being involved in the unfavorable decrease in SVR during hypovolemia.
Recently, it was suggested that autonomic function deteriorates *during* HD (12, 13, 14). Analysis of HRV with spectral analysis showed no increase in sympathetic tonus during HD in hypotensive patients. However, no age-matched groups were studied and, therefore, it cannot be excluded that the differences between the groups were due to an age-dependent decline in autonomic function. Furthermore, differences in sympatho-vagal balance were present at the start of HD, suggesting differences in basal autonomic status. In contrast, Ligtenberg and coworkers reported no change in autonomic function during HD, neither in stable nor in hypotensive patients (25). Thus, additional research with spectral analysis of HRV during HD is required to elucidate the role of autonomic dysfunction as a cause of intradialytic hypotension, with age-matched patient groups and simultaneous monitoring of intradialytic hemodynamics. Although age-dependency in autonomic function has often been observed, age-corrected reference values still are scarcely described and consensus about standard reference values has not been reached so far. Our data confirm the age-dependency of autonomic function by strongly significant negative correlations between the four autonomic variables and age.
Finally, it was remarkable in our study that the change in measured TBW between the start and the end of HD considerably overestimated the total UF volume (see Table 2). This might be due to excretion of electrolytes during HD, reducing total ionic mass. Impedance measurements depend upon the conductance of an electrical current by electrolytes in TBW. Loss of electrolytes results in a higher electrical resistance. Since electrical resistance and TBW are inversely correlated, calculated TBW at the end of HD will be underestimated.
To conclude, age-matched hypotensive and stable hemodialysis patients are identical in basal autonomic function at rest. Nevertheless, hypotensive patients decrease significantly more in SVR during HD. There was a highly significant relation between blood pressure and SVR variation, but no causal relationship could be established between basal autonomic function tests and blood pressure or SVR variation during HD. This suggests a different underlying cause for the fall in SVR than autonomic dysfunction at rest. Furthermore, with a combination of electrical impedance cardiography and on-line blood volume monitoring it is possible to guard dialysis patients non-invasively during hemodialysis with respect to intradialytic hemodynamics, possibly combined with autonomic function testing.

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6

The effect of profiled hemodialysis on intradialytic hemodynamics when a proper sodium balance is applied

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ABSTRACT

Background. Profiled hemodialysis has been claimed to ameliorate intradialytic complications such as hypotension. Frequently, these profiles are based on providing the patient with an accumulating sodium load. This increases the risk on *inter*dialytic complications, such as hypertension and increased weight gain. The present study investigated the effect of profiled hemodialysis, without an accompanying sodium loading, on *intra*-dialytic hemodynamics in stable hemodialysis patients.
Methods. In eight stable hemodialysis patients a standard dialysis (S-HD) was compared to a decreasing Na^+-profiled dialysis (Na-HD), and an ultrafiltration profiled dialysis (UF-HD). Care was taken to have the sodium balances similar during these sessions. The patients were monitored non-invasively during dialysis with respect to their cardiac performance by means of electrical impedance cardiography, their variation in blood volume by means of an on-line optical measurement, and their hydration state by means of body impedance analysis.
Results. The sodium balance and the mean arterial sodium concentrations were similar in the three treatments. Intradialytic hemodynamics during UF-HD were similar to those of S-HD. However, Na-HD improved blood pressure preservation, remarkably without significant blood volume preservation, due to a better stroke volume preservation in the first hour of dialysis.
Conclusion. Sodium-balanced, Na-profiled hemodialysis improves blood pressure preservation in stable hemodialysis patients without providing the patients with a sodium load. This effect is due to a better stroke volume preservation early in dialysis, without a significant reduction in blood volume decrease. UF-HD, as mono-therapy, has no beneficial effect on intradialytic hemodynamics in stable patients.

INTRODUCTION

Intradialytic hypotension remains one of the main problems during hemodialysis (HD), resulting in discomfort for the patient as well as reduced dialysis efficacy. Although its causes are still debated, various efforts have been made to prevent or predict hypotensive episodes in the individual patient. In recent years, profiled hemodialysis has gained increasing interest as a simple method to reduce hypotensive episodes. Decreasing ultrafiltration (UF) profiles aim at a better blood volume (BV) preservation by extracting the major part of the total UF volume in the first part of HD, when the patient is the most overhydrated. Profiles with a decreasing sodium concentration in the dialysate are thought to linearise the inevitable osmotic differences between the intra- and extracellular compartments by exchanging removed urea for sodium. Water inflow into the intracellular compartment is hereby avoided or diminished, and capillary refill will thus be optimised. However, most applied sodium profiles are based on providing the patient with a sodium overload, starting with a high dialysate sodium which decreases during dialysis until the normal sodium concentration used in standard HD. It is well known that most HD patients require antihypertensive medication, that more than 60% have left ventricular hypertrophy, and that the main cause of death is of cardiovascular origin (1). Notwithstanding these facts, in many studies an adequate sodium balance throughout the dialysis session was not calculated. It was assumed that sodium balance did not change, generally based on the findings that interdialytic complications hadn't increased significantly. In these studies, relevant parameters were frequently not provided, such as intradialytic hemodynamics, pre- and postdialytic sodium concentration, sodium balance, and blood volume variation (2-9).
The present study was designed to evaluate the value of profiling while maintaining a similar sodium balance in all applied dialysis modalities. A decreasing UF-profile, a decreasing Na-profile, and a standard hemodialysis were compared in eight stable patients on chronic intermittent hemodialysis. Hemodynamically stable patients were studied to investigate physiological effects of profiled HD on *intra*dialytic hemodynamics. Variations in BV, mean arterial pressure (MAP), stroke volume (SV), heart rate (HR), cardiac output (CO), and systemic vascular resistance (SVR) were assessed. In addition, pre- and postdialysis sodium concentration were recorded as well as afferent and efferent sodium flux, in order to monitor the sodium balance.

SUBJECTS AND METHODS

Subjects

Eight stable patients (2F/6M; mean age ± SEM: 63 ± 6 years) on chronic intermittent hemodialysis for on average 30 months (range: 2 - 68) were enrolled in this study. Dry body weight was determined individually by the attending physician on clinical grounds such as blood pressure, absence of peripheral and/or pulmonary oedema, and central venous pressure. Ultrafiltration volume was based on the difference between predialysis and dry weight. Patients experiencing a symptomatic decrease in supine systolic blood pressure of >30 mmHg or an absolute systolic blood pressure of < 90 mmHg during dialysis, accompanied by hypotensive symptoms such as dizziness, frequent yawning or perspiration, were defined as hypotensive. Patients enrolled in this study were considered to be hemodynamically stable, i.e. no occurence of symptomatic hypotension in the prior 10 dialysis sessions. All but two patients used antihypertensive drugs,

such as a-blockers, Ca-antagonists and ACE-inhibitors. No nitrates were used, and 3 patients used ß-blockers. To minimize confounding, antihypertensive medication was withheld on the day of dialysis. Withdrawal of this medication during a larger period was clinically not acceptable. None of the patients suffered from clinically manifest cardiovascular disease during the course of the study. Informed consent was obtained from all patients.

Dialysis modalities

All patients were dialysed three times 4 hours per week with biocompatible polysulfone membranes of 1.8 m^2 (Fresenius AG, Bad Homburg, Germany) on the Integra dialyzer (Hospal International, Lyon, France), using bicarbonate as buffer and heparin as anticoagulant. Blood flow was set at 250 ml/min, whereas the dialysate flow was 500 ml/min, with a constant dialysate temperature of 37.0° C. Blood samples were drawn from the arterial as well as the venous bloodline. Na^+ was determined at the beginning of the session and hourly thereafter, whereas urea and creatinine were assessed at the start and at the end of each session. All efferent dialysate was collected hourly, in which Na^+ and urea were measured. The collection of the efferent dialysate was performed by leading the waste-tubes to a water container, which was weighed hourly and emptied after taking a stirred sample for sodium determination. Afferent dialysate was sampled from a machine-integrated port for Na^+. Sodium determination was performed by the hospital laboratory using ion sensitive electrodes. Kt/V was calculated according to Daugirdas (10):

Kt/V = -ln (R - 0.03 - 0.75 * UF volume (l) / post HD weight (kg))

The afferent Na^+ load was calculated as $[Na^+]_D * Q_D$, where $[Na^+]_D$ is the sodium concentration in the dialysate (in mmol/L) and Q_D the dialysate flow (in ml/min), defined as the collected dialysate volume minus the UF volume to correct dialysate pump deviances. The efferent Na^+ load was calculated as $[Na^+]_c * volume_c$, where $_c$ stands for the collected dialysate. Finally, the Na^+ balance was the difference between the afferent and efferent Na^+ load.

Three different types of HD were applied to the patients, in random order but on the same day of the week for each patient to prevent differences by alternating interdialytic intervals:

1) One standard HD (S-HD), with a standard dialysate conductivity of 14.1 mS/cm similar to a sodium concentration of 141 mmol/L;

2) One HD with a decreasing UF-profile (UF-HD), whereby 40% of the total UF volume was removed in the first hour, and 20%, 30%, and 10% respectively in the second, third and fourth hour. The conductivity was kept constant at 14.1 mS/cm;

3) One HD with a decreasing Na^+-profile (Na-HD), containing a dialysate conductivity of 15.2 mS/cm (= 152 mmol/L) in the first hour, followed by 13.7 (= 137 mmol/L), 14.5 (= 145 mmol/L), and 13.0 mS/cm (130 mmol/L) in the remaining three hours, respectively. Averaged over the entire HD session, the mean dialysate conductivity of the Na-profile was 140.7 mmol/L and therefore equalled the dialysate conductivity of the standard HD session.

Both the decreasing UF- and Na-profiles were not established according to a linear model, but to an alternating model. This was done in order to facilitate differentiation in induced changes in hemodynamic variables as a result of the profiles, due to the hereby-increased differences between the hourly steps.

Table 1. *Sodium dynamics in the three hemodialysis modalities.*

	Standard HD	UF-profile	Na-profile
$[Na^+]_{art}$ (mmol/L)	140.1 ± 0.7	140.0 ± 0.7	140.8 ± 0.6
$[Na^+]_D$ (mmol/L)	140.0 ± 0.8	140.2 ± 0.9	140.7 ± 0.8
Na^+ load aff. (mmol)	16736 ± 91	16655 ± 81	16692 ± 190
Na^+ load eff. (mmol)	17098 ± 126	17094 ± 100	17051 ± 186
Na^+ balance (mmol)	-362 ± 66	-440 ± 68	-359 ± 0.38

Values are expressed as their mean ± SEM. No significant differences compared to standard HD. $[Na^+]_{art}$ = mean arterial sodium concentration; $[Na^+]_D$ = mean dialysate sodium concentration.

Hemodynamic variables

Blood pressure was recorded using an automatic cuff sphygmomanometer every 30 minutes and on occurrence of symptoms of hypotension, such as dizziness, muscle cramps, perspiration, or frequent yawning. Blood volume variation was monitored by means of an on-line optical device (Critline®, In-Line Diagnostics, Riverdale (Utah), USA), based on the non-invasive and continuous measurement of changes in hematocrit, which is inversely correlated to BV variation (11). Erythrocyte counts, hematocrit, hemoglobin concentration and red cell indices were performed on hourly drawn arterial blood samples as control determinations of the BV monitoring. SV recordings were performed hourly utilising electrical impedance cardiography (IPG-104 impedance Mini-Lab by RJL Systems, Detroit, USA, and Equip Medikey, Gouda, The Netherlands), a valid, non-invasive, bedside method to determine SV based on intrathoracic changes in electrical resistance due to heart pumping (12-15). Simultaneous ECG recordings provided HR, and CO was calculated as SV * HR. In addition, SVR was obtained using the formula SVR = (MAP / CO) * 80, expressed as dynes/s/cm^{-5}.

Total body water

Total body water (TBW) and extracellular water (ECW) were assessed at the start and the end of treatment by means of the whole body impedance method according to Lukaski (16). TBW was expressed as percentage of the body weight. ECW was expressed as percentage of TBW. Intracellular water (ICW) was then calculated as the difference between TBW and ECW, again expressed as percentage of TBW. For all three compartments relative changes from the start until the end of the treatment were calculated, expressed respectively as dTBW, dECW, and dICW (all in %).

Statistical analysis

Paired Student's t-test was used to test for differences in the two profiled dialyses compared to the standard HD, provided a normal distribution. The time effect of dialysis on hemodynamics per dialysis mode and changes in time between different dialysis modalities were analysed by means of repeated measures analysis of variance, again provided a normal distribution. *P* values < 0.05 were considered significant. When performing nonparametric tests, no differences in results were found.

RESULTS

Intradialytic complications requiring interventions occurred in three of the 24 treatments. One patient experienced a sudden hypotension at three hours of the S-HD. Another patient, in 10 previous HD sessions without complications, faced a hypotension necessitating saline infusions in the last 15 minutes of the S-HD, while in the Na-HD severe cramps occurred requiring cessation of dialysis. The Kt/V (mean 1.07 ± 0.02 SEM, range 0.80-1.32) did not differ between the three sessions and neither did the total UF volume (mean 2.8 ± 0.1 SEM, range 1.0-4.2). Concerning the sodium dynamics, the patients did not differ significantly between the three dialysis modalities in arterial Na^+ concentration and Na^+ balance (see Table 1). Concerning the intradialytic hemodynamic variables, Table 2 shows the absolute values at the start and at the end of treatment. The decrease in MAP was significantly more pronounced in S-HD compared to Na-HD ($p = 0.03$), but not compared to UF-HD ($p = 0.11$). Moreover, MAP decreased significantly during S-HD ($p < 0.05$), whereas it stabilised during Na-HD. The differences in MAP between S-HD and Na-HD were most pronounced after three hours of HD ($p < 0.05$), noticeably the moment when most hypotensions occur (see figure 1). Remarkably, BV decrease did not improve in Na-HD compared to S-HD. In the course of treatment dBV in the first hour during the UF-profile was significantly steeper in comparison to the rest ($p < 0.05$ for all) due to the vigorous UF rate (40% of total UF volume), although the milder UF rate in the remaining hours of HD equalised the total dBV over the entire session (see figure 2). However, during Na-HD an effect on SV was observed, mainly in the first hour of dialysis. Although the overall trend of SV from start until end of HD was not significantly different between Na-HD and S-HD ($p = 0.3$), the trend in the first hour of HD was highly significant ($p < 0.01$), as shown in figure 3. HR increased similarly during the three treatments, and, consequently, CO showed a tendency of a better preservation during Na-HD, although not significant ($p = 0.1$). SVR did not decrease significantly more during Na-HD, thus allowing for MAP preservation. An overview of changes in all hemodynamic variables is provided in Table 3. dTBW was equal between the groups in accordance with the similar UF volumes. However, differences in extracellular/intracellular fluid shifts were present. In UF-HD, the decrease in ECW was nearly significantly ($p = 0.06$) greater compared to S-HD and, consequently, the increase in ICW was more pronounced (UF-HD: 9.0 ± 1.2% versus S-HD: 6.2 ± 0.8%, $p = 0.03$). This suggests a greater intracellular water influx during the UF-profile. In contrast, during Na-HD dICW did not differ significantly from S-HD (Na-HD: 7.8 ± 3.7% versus S-HD: 6.2 ± 0.8, $p = 0.69$).

DISCUSSION

In the present study we compared in hemodynamically stable dialysis patients standard HD to HD with a decreasing UF-profile and HD with a decreasing Na-profile, with similar sodium balances. During dialysis, intradialytic cardiac performance, blood volume, and body hydration status were monitored non-invasively. It was shown that in stable patients sodium-balanced, profiled HD does have a beneficial effect on intradialytic hemodynamics, without the risk of providing patients with an accumulating sodium load. As was stressed in a recent report by Lam Sui Sang et al., a long-term increased mean dialysate sodium led to an amelioration of intradialytic symptoms in only 22% of the patients. It was accompanied by a significant increase in *inter*dialytic complications, such

as hypertension and increased weight gain, together with subjective discomfort due to increased thirst (17). In the present study, a better preservation of SV in the first hour of Na-HD led to a better blood pressure during the entire session. As changes in BV, HR and SVR did not differ from S-HD, a direct effect of Na-profiling on cardiac contractility might be postulated. Another important factor could be the venous compliance, which is shown to be reduced in hemodialysis patients, especially when they have hypertension (18). In this perspective, even a minimal improvement in BV preservation might lead to enhanced SV, due to the sometimes delicate relation between filling of the heart and cardiac output in cardiac-compromised patients. This suggests that cardiac-compromised HD patients could benefit especially from sodium-profiled HD. In that case, a sodium balance is even more important, as these patients are very sensitive to sodium loading.
An UF-profile would theoretically only lead to an better BV preservation if the mean UF rate is less than the individual maximum refill capacity, but in that case hypotensive episodes are unlikely to occur also during constant UF. As mono-therapy we could not prove any positive effect of UF-HD on BV and MAP preservation.
In the future, more studies with different and combined sodium-balanced profiles are needed, in large groups of stable and unstable patients and followed for a longer period of time. Nowadays non-invasive monitoring applications provide the opportunity to follow real-time events during HD, increasing the insight in the narrow margin of optimal effective dialysis and comfortable, patient-friendly dialysis.
In conclusion, sodium balanced Na-profiled hemodialysis improves blood pressure preservation in stable hemodialysis patients without providing the patients with a sodium load. The effect is due to a better stroke volume preservation early in dialysis, without a significant reduction in blood volume decrease. UF-HD, as mono-therapy, has no beneficial effect on intradialytic hemodynamics in stable patients.

Table 2. *Absolute hemodynamic variables at start and end of hemodialysis.*

	standard HD		UF-profile		Na-profile	
	start	end	start	end	start	end
MAP (mmHg)	94 ± 7	79 ± 5	105 ±5	94 ± 7	97 ± 4	91 ± 3
SVR ($dyn/s/cm^{-5}$)	2173 ± 490	2021 ± 404	2428 ± 422	2221 ± 388	2195 ± 398	2059 ± 351
CO (l/min)	4.3 ± 0.6	3.6 ± 0.4	4.1 ± 0.6	4.0 ± 0.6	4.4 ± 0.8	4.2 ± 0.6
SV (ml)	67 ± 10	50 ± 7	66 ± 12	57 ± 11	65 ± 11	54 ± 7
HR (bpm)	59 ± 4	74 ± 5	61 ± 5	76 ± 5	61 ± 4	79 ± 5
Erythrocytes (10^{12}/l)	3.54 ± 0.21	3.80 ± 0.25	3.58 ± 0.16	3.82 ± 0.17	3.60 ± 0.15	3.88 ± 0.20
UF_{tot} (l)		2.77 ± 0.28		2.91 ± 0.21		2.40 ± 0.82

All values are expressed as their mean ± SEM. No significant differences compared to standard HD

Table 3 *Relative changes in hemodynamic variables from the start until the end of hemodialysis*

	standard HD	UF-profile	Na-profile
dMAP (%)	-14.6 ± 5.9	-10.2 ± 5.4	-5.2 ± 4.9*
dSVR (%)	0.7 ± 9.8	-4.9 ± 7.7	-0.3 ± 8.8
dCO (%)	-11.0 ± 9.1	-1.6 ± 9.3	-1.0 ± 7.6
dSV (%)	-21.1 ± 7.2	-12.3 ± 9.6	-13.9 ± 6.1
dHR (%)	12.8 ± 4.9	13.4 ± 2.6	15.7 ± 5.0
dBV (%)	-6.3 ± 1.7	-6.2 ± 1.2	-6.8 ± 2.3

** = p < 0.05 compared to standard hemodialysis*

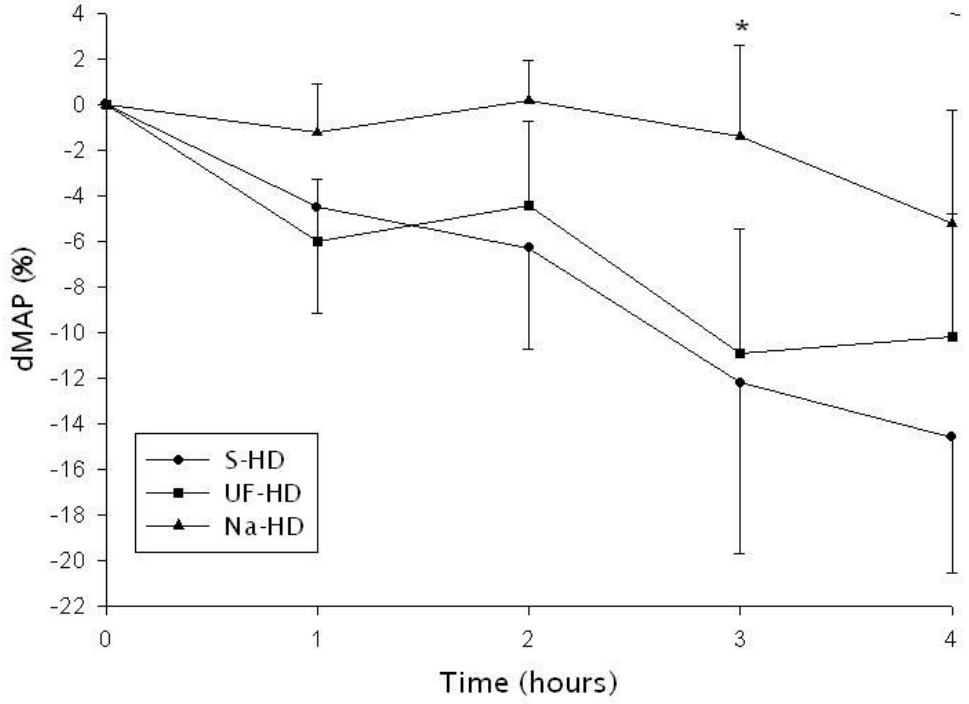

Figure 1. *Changes in mean arterial pressure (dMAP; mean ± SEM) during standard HD, Na-profiled HD, and UF-profiled HD, compared to the predialysis values. * = p < 0.05 compared to S-HD.*

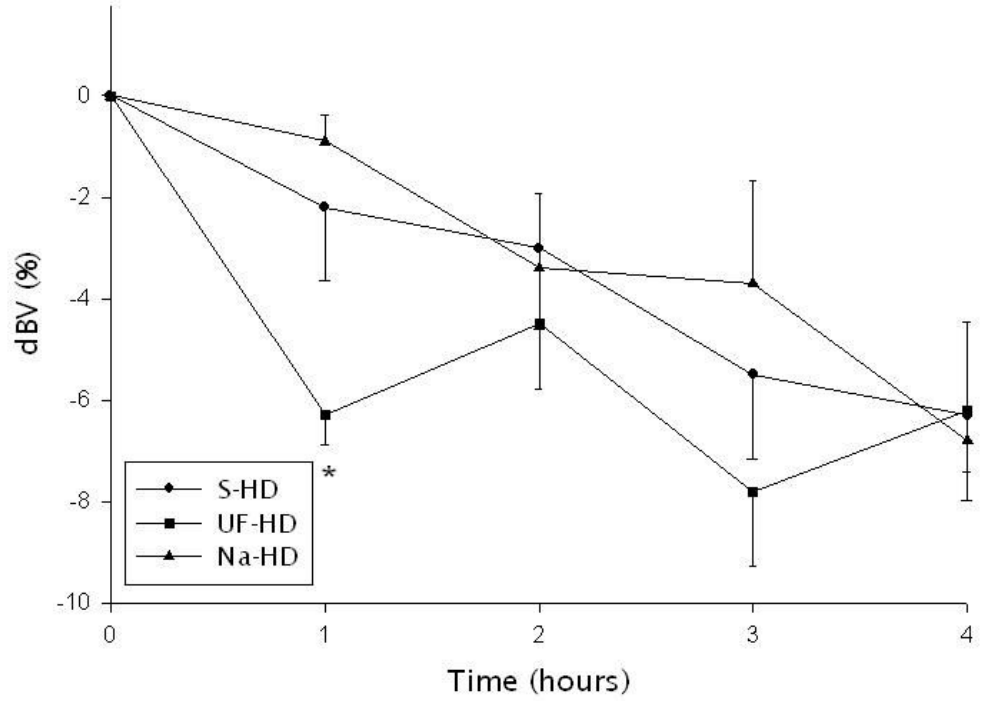

Figure 2. *Changes in blood volume (dBV; mean ± SEM) during standard HD, Na-profiled HD, and UF-profiled HD, compared to the predialysis values. * = p < 0.05 compared to S-HD.*

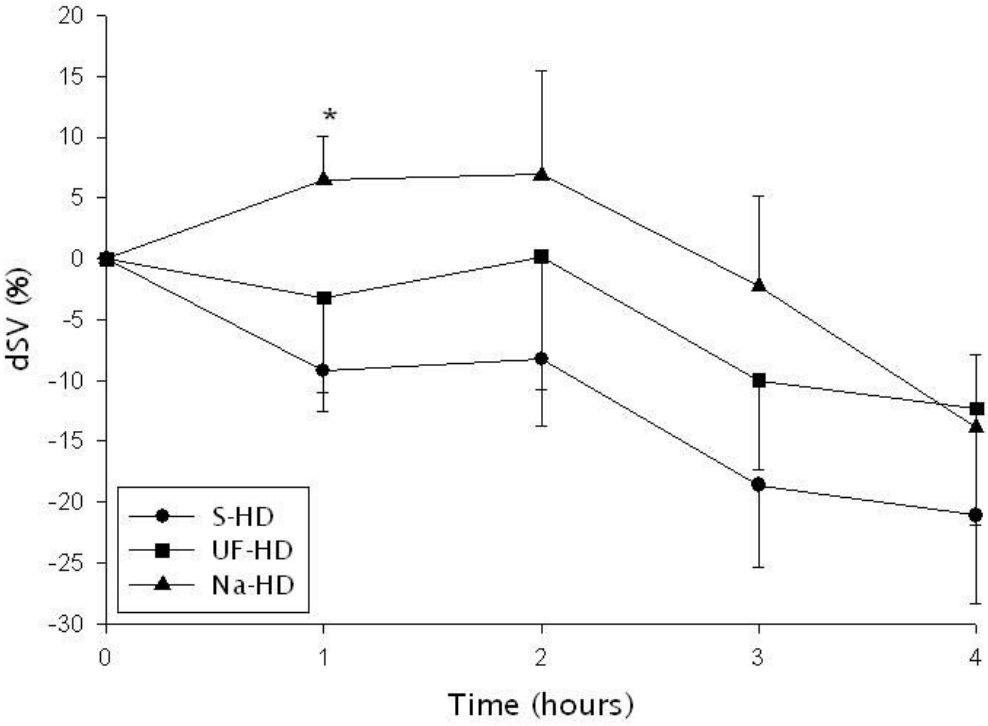

Figure 3. *Changes in stroke volume (dSV; mean ± SEM) during standard HD, Na-profiled HD, and UF-profiled HD, compared to the predialysis values. * = p < 0.05 compared to S-HD.*

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7

Summary

The aim of this thesis was to describe hemodynamics during hemodialysis by means of noninvasive bedside monitoring, in order to increase understanding of in intradialytic hypotension. Intradialytic hypotension is a common complication during standard hemodialysis, with an incidence of approximately 20 percent. It causes great discomfort to the hemodialysis patient and reduces dialysis efficacy because of necessary interventions such as interruption of hemodialysis and infusion of intravenous fluids. Because of changing patient characteristics with more emphasis on the elderly patient with more complex comorbidity, more individualized strategies to cope with intradialytic hypotension are needed. By gaining more insight in intradialytic hemodynamics, we hoped to enable classification of different subgroups in hypotension prone hemodialysis patients. In addition, tailor-made strategies to prevent intradialytic hypotension in these different groups could be proposed.

In c***hapter 1*** we provide an introduction into the physiology of hemodialysis-associated hemodynamics. Since several factors play a role whilst influencing each other, it is observed that a patient-friendly bedside method monitoring hemodynamic parameters during dialysis would be of great value. The technique of Electrical Impedance Cardiography is explained, as well as other applied noninvasive techniques for monitoring blood volume and hydration status. The aims for the studies performed in this thesis are defined.

Chapter 2 describes the noninvasive monitoring of hemodynamics during hemodialysis in a group of 68 chronic hemodialysis patients without manifest cardiac comorbidity. In 35 percent of hemodialysis sessions an hypotensive episode occurred after a mean dialysis duration of 3 hours. The predominant finding was a paradoxical decrease in systemic vascular resistance in the hypotensive group compared to a rise in systemic vascular resistance in de stable group. Remarkably, differences in blood volume decrease or cardiac output were of minor contribution.

In ***chapter 3*** the group of hypotensive hemodialysis patients was studied in more detail in order to see if a subgroup division could be made based on different patterns of hemodynamic responses to hemodialysis. It appeared that within the group of hypotensive patients a classification could be made into a subgroup with predominant decrease in systemic vascular resistance, and into a subgroup where the decrease in cardiac output prevailed. This discrimination of subtypes of intradialytic hypotension is important with respect to the possible prevention strategies.

However, it is questionable if the pathway leading to intradialytic hypotension is similar in different dialysis sessions within individuals. Therefore, in ***chapter 4*** we examined the reproducibility of intradialytic hypotension subgroups by monitoring several dialysis sessions in the group of hypotension prone patients. Although sometimes combined, we observed a clinical reproducibility of type of intradialytic hypotension of approximately 70 percent. This means that in 70 percent of dialysis sessions where a hypotensive episode occurred within an individual patient, the pathway of the causative mechanism was identical. This adds to the idea that hemodynamic monitoring during hemodialysis can contribute to a better insight in the needs of the individual patient, providing opportunities to tailor-made prevention strategies.

Since regulation of vascular tone is directed by the autonomic nervous system and autonomic neuropathy is a common finding in end stage renal disease patients due to long-term uremia, in ***chapter 5*** we investigated the function of the autonomic nervous system in hypotension prone and stable hemodialysis patients under normovolemic conditions. We found that autonomic dysfunction is present in all hemodialysis patients, although no differences between hypotension prone and stable patients could be observed. It was concluded that pre-existent autonomic dysfunction is not the cause of the severe decrease in systemic vascular resistance in hypotension prone hemodialysis patients compared to stable hemodialysis patients.

In ***chapter 6*** the effect of sodium and ultrafiltration profiling as a preventive strategy was studied. Care was taken to prevent sodium loading leading to increased thirst with the concomitant risk of extensive fluid accumulation. The hypothesis was tested if profiling of sodium or ultrafiltration leads to better a preservation of blood pressure. Ultrafiltration profiling did not show differences compared to standard hemodialysis. Sodium profiling however, appeared to improve blood pressure preservation mainly by a better stroke volume preservation early in dialysis, without a significant reduction in blood volume decrease. It was concluded that sodium profiling - when a proper sodium balance is used - can be a useful tool in prevention of intradialytic hypotension. Further research is needed to determine which subgroup of hypotension prone patients benefits most from sodium profiling.

Future perspectives

Several preventive strategies have been proposed to diminish the occurrence of intradialytic hypotension. The different strategies have different points of interaction, from increasing blood volume preservation to increasing arteriolar tone or cardiac contractility. Applying all available strategies to all hypotension prone hemodialysis patients is inefficient and might cause unnecessary discomfort for the patient. In order to provide the most appropriate strategy for the individual patient, patient derived data are to be acquired during hemodialysis. Closed-loop biofeedback systems are being introduced, offering information on blood volume course and dialysate electrolytes such as sodium.
However the most important hemodynamic parameters are not routinely available, such as stroke volume and systemic vascular resistance. Since there is a valid, non-invasive, bedside device for monitoring these parameters, incorporating hemodynamic monitoring in daily hemodialysis will improve insight in the dynamic compensatory mechanisms for the individual patient. With that information, refining of subgroup classification and specifying of preventive strategies can occur. Although long term, slow hemodialysis is to be preferred with respect to hemodynamic consequences of hemodialysis, current demands to medical science will not easily accept a time- and cost-consuming expansion of hemodialysis therapy provided today. Technology driven strategies aimed at improving individualized efficiency for the hemodialysis patient will probably dominate in the future.

8

Samenvatting

Bloeddrukdaling tijdens nierdialyse.

Niet-bloedige metingen van bloedsomloopbepalende factoren.

Achtergrond

In Nederland zijn momenteel ongeveer 9500 mensen met chronisch nierfalen afhankelijk van enigerlei vorm van nierfunctievervangende therapie. Bij ongeveer 35% hiervan wordt het bloed gezuiverd met behulp van nierdialyse (hemodialyse), een methode die sinds de vijftiger jaren beschikbaar is. Gemiddeld komt een patiënt 3 keer per week naar het ziekenhuis om gedurende 4 uur het bloed van overtollig vocht en afvalstoffen te laten zuiveren door een dialyseapparaat. Een van de belangrijkste complicaties tijdens hemodialyse zijn plotselinge bloeddrukdalingen (hypotensie). Deze hypotensieve episoden zijn zowel vervelend voor de patiënt (bewustzijnsverlies, katergevoel, kramp), als voor de effectiviteit van dialyse, omdat de vochtonttrekking (ultrafiltratie) onderbroken moet worden en soms zelfs extra vocht toegediend moet worden. Momenteel treden dergelijke bloeddrukdalingen tijdens ongeveer 20% van de dialysesessies op.

De patiëntenpopulatie wordt in de loop der jaren steeds ouder en er is bij hen vaker sprake van bijkomende ziekten met een nadelige invloed op het hart- en vaatstelsel, zoals suikerziekte. Onderzoek in de laatste decennia laat zien dat de bloeddrukdalingen tijdens dialyse (intradialytische hypotensie of *IDH*) door diverse factoren veroorzaakt worden. Het onttrekken van teveel vocht in te korte tijd speelt zeker een rol, echter daarmee kunnen niet alle bloeddrukdalingen verklaard worden. Sommige onderzoekers hebben een verminderde hartfunctie aangetoond, terwijl anderen stoornissen in de zenuwregulatie van de bloedvaten vonden. Omdat er zoveel verschillende factoren een rol spelen, die elkaar ook nog beïnvloeden, is het van groot belang om de functie van hart en bloedvaten tijdens dialyse te meten. Dit is mogelijk met behulp van meetapparatuur die via een lijn in een groot bloedvat dicht bij het hart ingebracht wordt, zoals op de Intensive Care veel gebeurt. Tijdens dialyse is dit echter een veel te ingrijpende en omslachtige methode om bruikbaar te zijn in de dagelijkse praktijk. In ons onderzoek is gebruik gemaakt van *Elektrische Impedantie Cardiografie* (*EIC*), een meetmethode waarmee de functie van hart en bloedvaten te meten is. Met elke hartslag wisselt de hoeveelheid bloed in de grote vaten in de borstholte. Veranderingen in deze hoeveelheid bloed zijn meetbaar doordat deze leiden tot veranderingen in de geleiding van een elektrisch stroompje dat door het *EIC* apparaat via 9 elektrodestickers op de huid aan de patiënt wordt toegediend. Deze methode is heel bruikbaar gebleken om veranderingen in bloeddrukbepalende factoren binnen een persoon te meten.

In **hoofdstuk 1** wordt de achtergrond van de problematiek met betrekking tot bloeddrukdalingen tijdens dialyse beschreven. Tevens worden de toegepaste technieken vermeld. Daarnaast worden de doelen van het in dit proefschrift beschreven onderzoek weergegeven. De belangrijkste doelen waren het verder zoeken naar de oorzaken van bloeddrukdalingen tijdens hemodialyse met behulp van patiëntvriendelijke, niet-bloedige meetmethoden, alsmede het blootleggen van eventuele verschillende oorzaken binnen de patiëntengroep waarin deze complicatie veel voorkomt. Uiteindelijk wordt gestreefd naar een meer individueel toepasbare dialysebehandeling, met minimaal verlies van dialyse-effectiviteit en maximaal comfort voor de patiënt.

Hoofdstuk 2 beschrijft de hart- en vaatfunctie tijdens een dialysesessie van 68 chronische hemodialysepatiënten, gemeten met behulp van onder andere *EIC*. Bij 35% ontstond een symptomatische bloeddrukdaling, gemiddeld na 3 uur dialyseren. De voornaamste bevinding was een daling van de vaatweerstand in deze hypotensieve groep, in tegenstelling tot een stijging bij de stabiele patiënten, zoals gebruikelijk is ten tijde van bloeddrukdalingen. Opvallend was dat bloedvolumedaling en verandering van hartminuutvolume een minder belangrijke rol speelden in de totale groep hypotensieve patiënten.

In **hoofdstuk 3** werd de groep hypotensieve patiënten in detail bestudeerd, met als doel om een eventueel onderscheid te kunnen maken op basis van verschillende vormen van hart- en vaatreactie op de hemodialyse. Het bleek dat binnen de groep hypotensieve patiënten een classificatie gemaakt kon worden in een groep met voornamelijk een daling in vaatweerstand en in een groep waar een daling in hartminuutvolume op de voorgrond stond. Dit onderscheid is belangrijk voor de ontwikkeling van mogelijke strategieën om bloeddrukdalingen tijdens hemodialyse te voorkómen. Verschillende oorzaken vergen immers een verschillende aanpak.

Gezien de verschillende typen van hypotensie rees **in hoofdstuk 4** de vraag of een hypotensieve patiënt tijdens verschillende dialysesessies steeds hetzelfde type bloeddrukdaling liet zien, met ander woorden of het type *IDH* reproduceerbaar was. Om deze reden werden instabiele patiënten gedurende 5 hemodialysesessies gemeten. Alhoewel er incidenteel een combinatie van de twee typen hypotensie voorkwam, was in 70% van de hypotensieve episoden binnen één patiënt het type bloeddrukdaling hetzelfde. Deze bevinding bevestigt de gedachte dat metingen van hart- en vaatfunctie tijdens dialyse een belangrijke bijdrage kunnen leveren aan het in kaart brengen van de oorzaken van bloeddrukdalingen bij de individuele patiënt. Hierdoor kan beter ingespeeld worden op de specifieke behoeften van de dialysepatiënt qua preventieve strategieën.

Omdat de vaatweerstand gereguleerd wordt door het onwillekeurige - of autonome - zenuwstelsel, hebben we in **hoofdstuk 5** onderzocht hoe de functie van dit deel van het zenuwstelsel functioneerde in rust bij zowel stabiele patiënten als patiënten met een neiging tot bloeddrukdalingen. Bij mensen met nierfalen is het autonome deel van het zenuwstelsel frequent aangetast door langdurig hoge waarden van afvalstoffen zoals ureum, welke normaliter met de urine uitgescheiden zouden worden. Met behulp van een aantal eenvoudige oefeningen is het reactievermogen van het autonome zenuwstelsel betrouwbaar te testen. Het bleek dat functiestoornissen van dit autonome zenuwstelsel voorkomen bij veel chronische nierpatiënten, echter er werd geen verschil waargenomen tussen de stabiele en de hypotensieve patiënten. Er werd geconcludeerd dat in rust bestaande stoornissen in de functie van het autonome zenuwstelsel geen verklaring vormden voor het optreden van bloeddrukdalingen tijdens hemodialyse.

In **hoofdstuk 6** werd de effectiviteit getest van een veel toegepaste preventieve strategie om *IDH* te voorkomen. Deze methode maakt gebruik van *natriumprofilering*, oftewel het veranderen van de concentratie zout in het badwater tijdens dialyse. Om te zorgen dat tijdens dialyse alleen overtollige stoffen worden uitgewassen, maar niet de nuttige

zouten, worden aan het badwater verschillende stoffen toegevoegd. Een van deze stoffen is natriumzout, dat in de bloedvaten water vanuit de weefsels kan aantrekken en dus kan zorgen voor een betere vaatvulling en daarmee stabielere bloeddruk. Echter, als er teveel natrium vanuit het badwater naar de patiënt gaat zorgt dit na de dialyse voor meer dorst en een te grote vochtinname. Bij een volgende dialyse moet er dan een (te) grote hoeveelheid water onttrokken worden, wat weer een hoger risico op hypotensie met zich meebrengt. Door de natriumconcentratie te veranderen van hoog in het begin, naar laag aan het eind van dialyse, kan gezorgd worden voor het belangrijke voordeel van extra bloeddrukondersteuning, zonder bijwerkingen als zoutoverbelasting.

In ons onderzoek zorgden we voor een gelijkblijvende zoutbelasting, terwijl de natriumconcentratie varieerde op verschillende wijzen tijdens dialyse. Ook de snelheid van ultrafiltratie – of vochtonttrekking – werd gevarieerd, wat echter geen beter bloeddrukbehoud opleverde. Het *natriumprofileren* verbeterde de bloeddruk wel ten opzichte van een standaard hemodialyse. Dit was te danken aan een verbeterd slagvolume van het hart, zonder een significante vermindering van bloedvolumedaling. Er werd geconcludeerd dat *natriumprofilering* een nuttige strategie ter voorkoming van *IDH* zou kunnen zijn.

Toekomstperspectief

Vele preventieve strategieën zijn reeds voorgesteld om het optreden van intradialytische hypotensie te verminderen. De werkingsmechanismen verschillen van verbeterd behoud van bloed volume, tot verhoging van vaatweerstand en verbetering van de contractiliteit van het hart. Het toepassen van diverse strategieën tegelijkertijd bij alle patiënten met neiging tot *IDH* is inefficiënt en kan leiden tot onnodige discomfort voor de patiënt. Om de meest geschikte strategie per patiënt te bepalen is het noodzakelijk om individuele gegevens over de functie van hart en vaten tijdens hemodialyse te verzamelen. Alhoewel er reeds terugkoppelingssystemen op de dialyseapparaten beschikbaar zijn, worden de belangrijkste bloeddrukbepalende factoren nog niet routinematig gemeten. Met de *Elektrische Impedantie Cardiograaf* is een methode beschikbaar waarmee deze variabelen aan het bed op patiëntvriendelijke wijze betrouwbaar gevolgd kunnen worden. Routinematig gebruik hiervan zal het inzicht in de individuele behoeften van de dialysepatiënt vergroten, leidend tot een betere toepassing van beschikbare preventieve strategieën. Alhoewel langere en daarmee geleidelijker verlopende dialysesessies veel bloeddrukschommelingen zouden kunnen voorkomen, is dit qua beschikbare tijd en plaatsen niet altijd realiseerbaar. Technische verbeteringen en geïndividualiseerde zorg kunnen die leemte opvullen. Daarop zal toekomstig onderzoek gericht moeten zijn.

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Bart Straver werd op 6 mei 1972 geboren in Alkmaar. Van 1984 tot 1990 doorliep hij het Murmellius Gymnasium te Alkmaar, waarna aangevangen werd met de studie Geneeskunde aan de Vrije Universiteit te Amsterdam.
Na het doctoraalexamen in 1995 werkte hij 3 jaar als onderzoeker op de afdeling Nefrologie in het VUMC (hoofd: prof.dr. A.J.M. Donker, later prof.dr. P.M. ter Wee), waar uiteindelijk de basis gelegd werd voor het hier beschreven onderzoek.
Van 1998 tot 2000 werden de co-assistentschappen doorlopen (cum laude) waarna hij een korte periode als keuringsarts gewerkt heeft.
Per 2001 startte hij de opleiding Kindergeneeskunde in het VUMC (opleider: prof.dr. J.J. Roord, later prof.dr. W.P.F. Fetter), waarbij anderhalf jaar doorgebracht werd in het St. Elisabeth Ziekenhuis te Tilburg (opleider: dr. P.J. van Dijken).
Sinds oktober 2005 is hij in opleiding tot kindercardioloog in het AMC te Amsterdam (opleider: prof.dr. J. Ottenkamp).